

**Optimizing Catalyst Reactivity, Separation, and Recycle in Processes Involving the  
Palladium-Catalyzed Suzuki Coupling of Heteroaromatic Compounds**

A Thesis  
Presented to  
The Academic Faculty

By

James “Corbett” Senter

In Partial Fulfillment  
Of the Requirements for the Degree  
Doctor of Philosophy in Chemical Engineering

Georgia Institute of Technology

August 2016

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Thesis Committee

Dr. Charles Liotta  
School of Chemical and Biomolecular  
Engineering  
*Georgia Institute of Technology*

Dr. Stefan France  
School of Chemistry and Biochemistry  
*Georgia Institute of Technology*

Dr. Ryan Lively  
School of Chemical and Biomolecular  
Engineering  
*Georgia Institute of Technology*

Dr. Jason Fisk  
Process Chemistry and Development  
*The Dow Chemical Company*

Dr. Carsten Sievers  
School of Chemical and Biomolecular  
Engineering  
*Georgia Institute of Technology*

Approved: May 17<sup>th</sup>, 2016

*To Family, Friends, and Colleagues, for supporting me, through the good times and bad.*

## ACKNOWLEDGEMENTS

I am sincerely grateful for having the chance to work with Dr. Charles Liotta, my graduate advisor. His guidance, both in research and in life, has proven incredibly valuable throughout my time in grad school. His background in chemistry and experience working with engineers provided a unique environment in which to sharpen my skills as a scientist. His positivity and good-natured (I think) humor also helped to keep things in perspective when things became difficult.

Dr. Pamela Pollet is also someone whom I am fortunate to have worked with. Her experience working with many Chemistry and Chemical Engineering students proved tremendously valuable in navigating through various obstacles which have arisen in grad school. Additionally, I am very grateful for her availability and willingness to serve as a soundboard for even my most ridiculous ideas.

Dr. Eckert also deserves a special thanks. He is the one who originally hired me into the group. While I did not get to work with him as much as I would have liked, I still enjoyed the advice given from his years of experience advising students.

My family and friends deserve special thanks. My family's unyielding support and honest advice have been invaluable, not only in grad school, but throughout my life, and my friends have proven a tremendous outlet for when I needed a break from the lab.

The contributions of my colleagues in the Liotta Group also deserve recognition. Dr. Wilmarie Medina-Ramos, Dr. Wes Woodham, Dr. Mark Conley, Dr. Esteban Ureña-Benavides, Dr. Steve Saunders, Dr. Amber Rumple, David Hule, Jonathan Slater, Lily-Cheng, and Alex Aw all stand out for their contributions to my graduate education.

Finally, I would like to thank our collaborators at the Dow Chemical Company, specifically, Bruce Holden and Dr. Jason Fisk. Their guidance in research was critical not only in driving my research, but offering a unique perspective into how projects are approached in industry.

## TABLE OF CONTENTS

ACKNOWLEDGEMENTS .....	iv
LIST OF TABLES .....	x
LIST OF FIGURES .....	xii
LIST OF EQUATIONS .....	xx
LIST OF SCHEMES .....	xxi
LIST OF ABBREVIATIONS .....	xxii
CHAPTER 1 - Introduction .....	25
1.1 Principles of Green Chemistry and Engineering .....	25
1.2 The Effect of CO <sub>2</sub> and pH on the Suzuki Coupling of Basic, Nitrogen-Containing Compounds .....	28
1.3 Use of Organic-Aqueous Tunable/Smart Solvents to Recover and Recycle Palladium Catalysts .....	30
1.4 References .....	33
CHAPTER 2 - Effect of CO <sub>2</sub> and Ph on the Suzuki Coupling of Basic, Nitrogen- Containing Compounds .....	35
2.1 Introduction .....	35
2.1.1 Overview and Importance of the Suzuki Coupling Reaction .....	35
2.1.2 Mechanism of the Suzuki Reaction .....	36
2.1.3 Challenges of the Suzuki Reaction .....	38
2.2 Experimental .....	44
2.2.1 Materials .....	44

2.2.2 Experimental Procedure.....	44
2.2.3 Analyses.....	55
2.3 Results and Discussion .....	63
2.3.1 The effect of CO <sub>2</sub> and Volume Percent of Water .....	63
2.3.2 Effect of pH on Reaction .....	69
2.3.3 Reaction Progress as a Function of Time .....	71
2.3.4 Effect of Phenylboronic Acid Concentration.....	76
2.3.5 Early Reaction Behavior/Catalyst Tracking .....	80
2.4 Conclusions.....	84
2.5 References.....	87
CHAPTER 3 - Recovery of Palladium from Suzuki Coupling Mixtures Using	
Organic/Aqueous Tunable Solvents (OATS) and Sulfur-Containing Additives.....	89
3.1 Introduction.....	89
3.1.1 Suzuki Coupling Reaction .....	89
3.1.2 Separation of Pd from Suzuki Reaction Product. ....	90
3.1.3 OATS Technology .....	91
3.1.4 Application of OATS to Suzuki Systems .....	92
3.1.5 Selection of Suzuki Reaction.....	93
3.1.6 Selection of Additives.....	94
3.1.7 Substrate Scope Expansion.....	97
3.2 Experimental Section.....	98
3.2.1 Materials .....	98
3.2.2 Experimental.....	98

3.2.3 Instrumentation .....	108
3.3 Results and Discussion .....	109
3.3.1 2-Bromo-5-methylpyridine .....	109
3.3.2 4-Amino-2-bromopyridine.....	122
3.4 Conclusions.....	127
3.5 References.....	129
CHAPTER 4 - Recycle of Palladium Using Smart Solvents.....	132
4.1 Introduction.....	132
4.1.1 Suzuki Coupling .....	132
4.1.2 Catalyst Separation and Recycle Motivation.....	132
4.1.3 OATS .....	133
4.2 Experimental.....	136
4.2.1 Materials .....	136
4.2.2 Experimental .....	136
4.2.3 Instrumentation .....	146
4.3 Results and Discussion .....	149
4.3.1 5-Methyl-2-phenylpyridine. Process Optimization .....	149
4.3.2 Separation of Pd from 5-Methyl-2-phenylpyridine: Effect of pH and Acid Anion.....	165
4.3.3 Substrate Scope Expansion.....	169
4.3.4 Control Separations – 5-Methyl-2-phenylpyridine.....	197
4.4 Conclusions.....	203
4.5 References.....	208



CHAPTER 5 - Conclusions and Recommendations.....	210
5.1 Effect of CO <sub>2</sub> and pH on the Suzuki Coupling of Basic, Nitrogen-Containing Compounds .....	210
5.1.1 Conclusions.....	210
5.1.2 Recommendations.....	211
5.2 Palladium Recovery Using Organic-Aqueous Tunable Solvents (OATS).....	212
5.2.1 Conclusions.....	212
5.2.2 Recommendations.....	213
5.3 Recycle of Pd Using Smart Solvents .....	216
5.3.1 Conclusions.....	216
5.3.2 Recommendations.....	218
5.4 References.....	220
Appendix A - Process Mass Intensity and Process Cost Intensity of Separation and Recycle of Catalyst .....	221

## LIST OF TABLES

Table 1.1. 12 Principles of Green Chemistry <sup>4</sup> .....	26
Table 1.2. 9 Principles of Green Engineering <sup>5</sup> .....	27
Table 2.1. Buffer compositions for 4-amino-2-bromopyridine at 40% water. *Reagents and solvents were preconditioned with CO <sub>2</sub> then purged and run under N <sub>2</sub> . ....	52
Table 2.2. Buffer compositions for 4-amino-2-bromopyridine at 25% water. ....	53
Table 2.3. Buffer compositions for 2-bromopyridine at 40% water.....	53
Table 2.4. Buffer compositions for 4-amino-2-chloropyridine at 40% water .....	54
Table 2.5. Buffer compositions for 2-chloropyridine at 40% water .....	55
Table 2.6. Reactions run for 24 hours with 4-amino-2-halopyridines and 2-halopyridines with 25% v/v of H <sub>2</sub> O. (a). Yield calculated from GC-FID calibration curve.....	64
Table 2.7. Reactions run for 24 hours with 4-amino-2-halopyridines and 2-halopyridines with 40% v/v of H <sub>2</sub> O. (a). Yield calculated from GC-FID calibration curve.....	67
Table 3.1. Separation results of additive screening experiments. <sup>1</sup> Corresponds to additive in Figure 3.3. 5-methyl-2-phenylpyridine.....	111
Table 4.1. Separations with toluene. Follows Figure 4.14 but only 20mL H <sub>2</sub> O added following decantation and 5mL Toluene added instead of CO <sub>2</sub> pressure.....	153
Table 4.2. Addition of TPP to separation system. Separation performed with 5eq. EDTA. ....	161
Table 4.3. Post-Recycle Separations. Prod: 5-methyl-2-phenylpyridine.....	164
Table 4.4. TOF of recycle reaction for different acids used for separation. ....	168

Table 4.5. Recycle reaction of Pd separated from 2-phenylpyridine compared to fresh reaction.....	173
Table 4.6. Summary of recycle reactions run for Pd separated from 6-amino-2-phenylpyridine .....	176
Table 4.7. Separation of Pd from 5-cyano-2-phenylpyridine. SM = 5-methyl-2-bromopyridine. Prod = 5-methyl-2-phenylpyridine. Separations carried out using HCl. ....	193

## LIST OF FIGURES

Figure 1.1. Market Deficit of Palladium (in ‘000s of oz.), forecast to 2020. <sup>31</sup>	30
Figure 2.1. Generalized Suzuki coupling reaction.	35
Figure 2.2. Gleevac <sup>TM</sup>	36
Figure 2.3. Suzuki coupling mechanism.	37
Figure 2.4. Formation of bis (aminopyridine) palladium complexes which are less reactive towards cross-coupling reactions.	38
Figure 2.5. Yields and conjugate acid pK <sub>a</sub> of the coupling of various aminochloropyridines with phenylboronic acid. <sup>21</sup>	39
Figure 2.6. Acetyl protection of 3-amino-2-chloropyridine to promote reaction in Suzuki coupling. <sup>18</sup>	40
Figure 2.7. Dialkylbiaryl ligands developed by Buchwald to promote reactions of chlorinated substrates. <sup>10</sup>	41
Figure 2.8. Efficient coupling of aminochloropyridines utilizing ligand SPhos.	42
Figure 2.9. Reaction of CO <sub>2</sub> with water and base to form new aqueous phase composition.	43
Figure 2.10. <sup>1</sup> H NMR of 2-phenyl-4-aminopyridine.	50
Figure 2.11. <sup>13</sup> C NMR of 4-amino-2-phenylpyridine.	51
Figure 2.12. Example GC-FID spectra: reaction of 4-amino-2-bromopyridine with phenylboronic acid under 2 atm. CO <sub>2</sub> and 40% water after 24 h after workup. Calibration curves are used to relate the area of each peak to a concentration, which is then used to calculate yield and conversion.	56

Figure 2.13. GC-FID calibration curve of 4-amino-2-chloropyridine.....	57
Figure 2.14. GC-FID Calibration Curve for 4-amino-2-bromopyridine.....	58
Figure 2.15. GC-FID Calibration Curve for 2-phenylpyridine-4-ylamine. ....	58
Figure 2.16. GC-FID Calibration Curve for 2-chloropyridine. ....	59
Figure 2.17. GC-FID Calibration Curve for 2-bromopyridine. ....	59
Figure 2.18. GC-FID Calibration Curve for 2-phenylpyridine.....	60
Figure 2.19. Example $^1\text{H}$ NMR spectra: reaction of 4-amino-2-bromopyridine with phenylboronic acid under 2 atm. $\text{CO}_2$ with 40% water, 24 h, after workup. ....	61
Figure 2.20. Phase behavior of the Suzuki coupling system under nitrogen and carbon dioxide.....	66
Figure 2.21. Reaction of $\text{CO}_2$ with water and bases to form new inorganic phase composition.....	66
Figure 2.22. Yield as a function of pH for 4-amino-2-halopyridines and 2-halopyridines. Follows procedure in Scheme 2.1 except different bases are used in certain cases. ....	70
Figure 2.23 - 4-Amino-2-bromopyridine reaction progress as a function of time. % $\text{H}_2\text{O}$ is measured as %v/v. Time = 0 corresponds to the reaction system reaching temperature (Scheme 2.1). ....	73
Figure 2.24. Reaction progress as a function of time for 4-amino-2-halopyridines. Reactions run with 40% v/v water. Time = 0 corresponds to the reaction system reaching temperature (Scheme 2.1). ....	74
Figure 2.25. Suzuki coupling reaction of 4-amino-2-bromopyridine. Follows Scheme 2.1 except for where $\text{K}_2\text{HPO}_4$ is used as base.....	75

Figure 2.26. Reaction progress as a function of time for 2-chloropyridines. Follows Scheme 2.1. Reactions run with 40% v/v water. Time = 0 corresponds to the reaction system reaching temperature.....	76
Figure 2.27. Phenylboronic acid effect on 4-amino-2-bromopyridine reactions under CO <sub>2</sub> pressure. Scheme 2.2. X = Br. ....	78
Figure 2.28. Phenylboronic acid effect on 4-amino-2-chloropyridine reactions under CO <sub>2</sub> pressure. Scheme 2.2. X = Cl. Yield based on pyridine Substrate. ....	79
Figure 2.29. Early kinetic data. Follows Scheme 2.3. X = Br. ....	82
Figure 2.30. <sup>31</sup> P-NMR of sample taken from K <sub>2</sub> HPO <sub>4</sub> (pH: 8) reaction at 1 hour. ....	83
Figure 2.31. <sup>31</sup> P-NMR of sample taken from K <sub>3</sub> PO <sub>4</sub> (pH: 13) reaction at 1 hour. ....	84
Figure 3.1. Suzuki coupling reaction mechanism. <sup>8-9</sup> .....	90
Figure 3.2. Process Flow Diagram for OATS Implementation in Suzuki Coupling Processes.....	93
Figure 3.3. Additives screened for Pd removal.....	96
Figure 3.4. Schematic of Combinatorial Apparatus Built In-House for High-Pressure Sampling of Multiple Mixtures.....	99
Figure 3.5. Schematic of Parr Reactor Sampling Apparatus. ....	100
Figure 3.6. GC-FID Calibration of 5-methyl-2-bromopyridine.....	102
Figure 3.7. GC-FID calibration of 5-methyl-2-phenylpyridine.....	102
Figure 3.8. GC-FID calibration curve for 4-amino-2-bromopyridine. ....	103
Figure 3.9. GC-FID calibration curve for 4-amino-2-phenylpyridine.....	104
Figure 3.10. Height-volume calibration for the cathetometer.....	105

Figure 3.11. Baselined separation results as a function of CO <sub>2</sub> pressure. Prod = 5-methyl-2-phenylpyridine.....	110
Figure 3.12. Top Additives Screened for Separation of Pd from 5-methyl-2-phenylpyridine. <sup>29-32</sup> .....	113
Figure 3.13. Pd-chelant structures from literature. ....	114
Figure 3.14. Separation results of selected additives.....	116
Figure 3.15. Aqueous phase palladium content as a function of CO <sub>2</sub> pressure. Pd % is normalized for Pd in solution.....	118
Figure 3.16. Aqueous product content as a function of CO <sub>2</sub> pressure.....	119
Figure 3.17. Aqueous Phase Palladium Retention as a Function of Cysteine Loading..	121
Figure 3.18. Separation of Pd from 4-amino-2-phenylpyridine as a Function of CO <sub>2</sub> pressure. ....	123
Figure 3.19. Formation of Carbonic Acid via CO <sub>2</sub> Addition to Water and Subsequent Proton Exchange with 4-amino-2-phenylpyridine.....	124
Figure 3.20: Separation data of Pd from 4-amino-2-phenylpyridine using Cysteine as additive. Function of CO <sub>2</sub> pressure. Prod: 4-amino-2-phenylpyridine. ....	125
Figure 3.21. Separation data of Pd from 4-amino-2-phenylpyridine using thiourea as additive. Function of CO <sub>2</sub> pressure. Prod: 4-amino-2-phenylpyridine. ....	126
Figure 4.1. Rhodium-Catalyzed Hydroformylation of 1-octene.....	134
Figure 4.2. GC-FID calibration of 5-methyl-2-phenylpyridine.....	137
Figure 4.3. GC-FID calibration curve 2-bromopyridine.....	138
Figure 4.4. GC-FID calibration curve. 2-phenylpyridine. ....	138
Figure 4.5. GC-FID calibration curve for 4-amino-2-bromopyridine. ....	139

Figure 4.6. GC-FID calibration curve for 4-amino-2-phenylpyridine.....	140
Figure 4.7. GC-FID calibration curve of 6-amino-2-bromopyridine.....	141
Figure 4.8. GC-FID calibration curve of 6-amino-2-phenylpyridine. ....	141
Figure 4.9. GC-FID calibration curve. 4-bromoanisole.....	142
Figure 4.10. GC-FID calibration curve. 4-methoxybiphenyl. ....	143
Figure 4.11. GC-FID calibration curve. 2-bromo-5-cyanopyridine. ....	144
Figure 4.12. GC-FID Calibration Curve. TPP .....	147
Figure 4.13. GC-FID Calibration Curve. TPP-O.....	148
Figure 4.14. Process Scheme. *Following reaction, experiments performed a). 28 mL ACN and 42 mL H <sub>2</sub> O are added b). 20 mL H <sub>2</sub> O added.....	149
Figure 4.15. Post-reaction <sup>31</sup> P-NMR of Scheme 4.1.....	150
Figure 4.16. EDTA and Cysteine.....	151
Figure 4.17. Separation data under 400psi CO <sub>2</sub> pressure with 20 eq. (of Pd) of additive . Pd = palladium, prod = 5-methyl-2-phenylpyridine. <sup>1</sup> Excess ACN and H <sub>2</sub> O added to system prior to separation. 20 eq. of additives used. ....	152
Figure 4.18. Process of Multi-stage extraction using 5mL toluene. *% of total amount left following 1 <sup>st</sup> separation. 20mL H <sub>2</sub> O added at each separation stage.....	153
Figure 4.19. Recycle of Pd separated in Table 4.1/first separation. 4 hour Turnover frequency: 1 eq. TPP: 14, 10 eq. TPP: 23.....	154
Figure 4.20. Recycle of Pd separated in 2 <sup>nd</sup> extraction in Figure 4.18. ....	155
Figure 4.21. Separation scheme with wash step. ....	156
Figure 4.22. Wash-step separation. Function of CO <sub>2</sub> pressure. ....	157
Figure 4.23. CO <sub>2</sub> toluene separation comparison. Wash step.....	158



Figure 4.24. Separation as a function of EDTA eq. Toluene used as anti-solvent. ....	159
Figure 4.25. Separation experiments using 5eq. EDTA, Toluene during the washing step, and multiple washes. 20mL H <sub>2</sub> O is added at each stage.....	160
Figure 4.26. Recycle reaction summary. TOF = Turnover frequency (mmol Prod/mmol Pd/hours). Prod = 5-methyl-2-phenylpyridine. TPP = triphenylphosphine.....	162
Figure 4.27. Amount of Product and Pd in aqueous phase as a function of pH. Either HCl or EDTA used as additives. Follows separation in Figure 4.21, uses Toluene.....	166
Figure 4.28. Summary of separation vs. pH for different additives. Pd = Palladium, Prod = 5-methyl-2-phenylpyridine.....	167
Figure 4.29. Summary of separation vs. pH for different substrate systems. Prod (product) is pictured above result. All separations performed with 5eq EDTA. *Product pKa unavailable. **~15eq EDTA used as additive. ***1 eq. EDTA present. All compounds follow scheme in Figure 4.21 except 4-NH <sub>2</sub> -2phpyr compound. ....	170
Figure 4.30. Separation of 2-phenylpyridine as a function of Additive. Separation procedure follows Figure 4.21.....	172
Figure 4.31. Acidic separation of Pd from 6-amino-2-phenylpyridine. Follows procedure in figure.....	175
Figure 4.32. Separation of Pd from 6-amino-2-phenylpyridine using cysteine as an additive. Prod: 6-amino-2-phenylpyridine.....	177
Figure 4.33. Post-reaction <sup>31</sup> P-NMR Scheme 4.4.....	179
Figure 4.34. Separation of Pd from 4-amino-2-phenylpyridine under basic conditions using toluene as an anti-solvent. Prod: 4-amino-2-phenylpyridine.....	180

Figure 4.35. Hydrophobic acid additives used. A: perfluorooctanoic acid, B: paratoluene sulfonic acid C: Dodecylbenzenesulfonic acid. D: Heptylbenzene .....	181
Figure 4.36. Separation of Pd from 4-amino-2-phenylpyridine using hydrophobic acidic additives. Prod: 4-amino-2-phenylpyridine. A, B, C, and D refer to additives in Figure 4.35.....	182
Figure 4.37. Behavior of protonated product with hydrophobic additives. ....	183
Figure 4.38. Separation of Pd from 4-amino-2-phenylpyridine using hydrophobic additives at higher pH. A, B, and C refer to additives in Figure 4.35. ....	184
Figure 4.39. Separation of Pd from 4-amino-2-phenylpyridine using DBSA and chelating additive. A and C refer to additives in Figure 4.35.....	185
Figure 4.40. Separation of Pd from 4-amino-2-phenylpyridine using cysteine and base. ....	186
Figure 4.41. Separation data for separation of Pd from 5-cyano-2-phenylpyridine. Separation procedure uses wash step. Shows amount of aqueous product and Pd. Prod: 5-cyano-2-phenylpyridine. ....	189
Figure 4.42. $^{31}\text{P}$ -NMR of organic phase following reaction. ....	190
Figure 4.43. *added at reaction temperature. **SM present from beginning. ***product from beginning. ****SM after wash step. ....	192
Figure 4.44. Post-reaction $^{31}\text{P}$ -NMR of Table 4.7 (SM present initially.).....	194
Figure 4.45. Separations with varying amounts of TPP present in reaction. ....	195
Figure 4.46. Post-reaction $^{31}\text{P}$ -NMR of reaction when 1 eq. TPP is present. ....	196
Figure 4.47. Control separation with Pd-tetrakis. SM= 5-methyl-2-bromo-pyridine.....	197

Figure 4.48. Control separation with 0.3 M of SM (5-methyl-2-bromopyridine) and Prod. (5-methyl-2-phenylpyridine). Separation performed in ACN,H <sub>2</sub> O, and toluene mixture. HCl used to adjust pH. ....	198
Figure 4.49. Control separation with 0.06 M of SM (5-methyl-2-bromopyridine) and 0.24M Prod. (5-methyl-2-phenylpyridine). Separation performed in ACN,H <sub>2</sub> O, and toluene mixture. HCl used to adjust pH. ....	199
Figure 4.50. Pd-DBA. ....	200
Figure 4.51. Control separation with 1mol% Pd-DBA. 0.3 M SM= 5-methyl-2-bromopyridine. ....	201
Figure 4.52. Control separation with 1mol% Pd-DBA. 0.3 M Prod= 5-methyl-2-phenylpyridine. ....	202
Figure 4.53. “Control Separation” using 5-methyl-2-phenylpyridine (80%), 5-methyl-2-bromopyridine (20%), and Pd-DBA (1mol%) in ACN,H <sub>2</sub> O, and toluene. HCl is used to adjust pH. ....	203
Figure 4.54. Post-reaction catalyst state possibilities. Ln = TPP or reaction product. ...	205
Figure 4.55. Effect of acid addition. Inserted Catalyst .....	205
Figure 4.56. Effect of acid addition: product complexation. ....	206
Figure 5.1. Oxidation of Cysteine to Cystine. ....	214
Figure 5.2. Protonation of 4-amino-2-phenylpyridine. ....	214
Figure 5.3. Hydrophobic Pd OATS scheme. ....	215
Figure 5.4. Potential Hydrophobic Additives .....	216

## LIST OF EQUATIONS

Equation 2.1. NMR Yield Calculation.....	61
Equation 3.1. ....	105
Equation 3.2. ....	106
Equation 3.3. Calculation of total amount of analyte (x) under CO <sub>2</sub> pressure. ....	106
Equation 4.1 ....	145
Equation 5.1. Equations for calculation of feed and recycle catalyst amounts at steady-state.. ....	223
Equation 5.2. Process Mass Intensity (PMI).....	224
Equation 5.3. Process Cost intensity.....	225

## LIST OF SCHEMES

Scheme 2.1. Suzuki Coupling Reaction Scheme. ....	63
Scheme 2.2. Reaction varying initial phenylboronic acid concentrations. ....	77
Scheme 2.3. Modified Reaction Scheme. ....	81
Scheme 3.1. Suzuki coupling of 5-methyl-2-bromopyridine. ....	94
Scheme 3.2. Suzuki Coupling Reaction of 4-amino-2-bromopyridine with Phenylboronic Acid. ....	97
Scheme 4.1. Suzuki coupling reaction of 5-methyl-2-phenylpyridine. ....	150
Scheme 4.2. 2-bromopyridine reaction scheme. Reactions run for 4 hours. ....	171
Scheme 4.3. Reaction of 6-amino-2-bromopyridine with phenylboronic acid. ....	174
Scheme 4.4. Reaction scheme for Suzuki coupling of 4-amino-2-phenylpyridine with phenylboronic acid. ....	178
Scheme 4.5. Suzuki Reaction of 4-bromoanisole ....	187
Scheme 4.6. Suzuki reaction of 5-cyano-2-phenylpyridine. ....	188
Scheme 4.7. Potential effect of having 5-methyl-2-bromopyridine present in Suzuki reaction. ....	191

## LIST OF ABBREVIATIONS

ACN	acetonitrile
AA	Atomic Absorption
Aq	Aqueous Phase
Br	Bromo
Cl	Chloro
CO <sub>2</sub>	carbon dioxide
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
DOE	Department of Energy
GC-FID	gas chromatography – flame ionization detector
GC-MS	gas chromatography – mass spectrometry
HPLC	high-performance liquid chromatography
H <sub>2</sub> O	Water
LC-MS	liquid chromatography – mass spectrometry
NMR	nuclear magnetic resonance (spectroscopy)
NSF	National Science Foundation

N <sub>2</sub>	Nitrogen
Org	Organic Phase
Pd	Palladium
ppm	parts per million
Pyr	Pyridine
RevIL	reversible ionic liquid
RT	room temperature
Rxn	Reaction
THF	tetrahydrofuran
TOF	Turnover Frequency
TPP	Triphenylphosphine
TPPMS	Triphenylphosphine monosulfonate
TPPTS	Triphenylphosphine trisulfonate
UV-vis	ultraviolet-visible (spectroscopy)

## SUMMARY

This thesis uses the principles of Green Chemistry and Engineering to attempt to optimize processes involving palladium-catalyzed Suzuki coupling. The first project uses pH and CO<sub>2</sub> as parameters which improve the reactivity of basic, nitrogen-containing substrates in Suzuki coupling reactions without the use of expensive ligands or protection and deprotection steps.

The second project describes a novel catalyst separation process which uses additives and Organic-Aqueous Tunable Solvents (OATS). This process effectively separates palladium catalyst from basic, nitrogen-containing Suzuki reaction products.

The third project describes the separation and recycle of Pd catalyst following Suzuki coupling reaction. The technology uses OATS/Smart-solvents in combination with additives to separate Pd following Suzuki reaction and then re-use the catalyst in subsequent Suzuki chemistry.



## CHAPTER 1 - INTRODUCTION

### 1.1 Principles of Green Chemistry and Engineering

Since the passing of the National Environmental Policy Act (1969),<sup>1</sup> the field of “Green Chemistry” is frequently used as a tool for improving the interactions between the environment, the chemical industry, and the society that it serves. In the following decades, several important steps occurred in the field of green chemistry: the creation of the Environmental Protection Agency (EPA),<sup>2</sup> the passing of numerous pieces of environmental legislation, and a series of unfortunate chemical accidents.<sup>3</sup> However, the largest growth was not seen until nearly the end of the millennium.

Specifically, in 1998, Paul Anastas and John Warner laid the groundwork for what would become the foundation of understanding of green chemistry applications by publishing *Green Chemistry: Theory and Practice*.<sup>4</sup> Within this text, Anastas and Warner give 12 guidelines to encourage the development of sustainable chemistry. Those guidelines have come to be known as the 12 Principles of Green Chemistry (Table 1.1).

**Table 1.1. 12 Principles of Green Chemistry<sup>4</sup>**

C1	It is better to prevent waste than to treat or clean up waste after it has been created.
C2	Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
C3	Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
C4	Chemical products should be designed to affect their desired function while minimizing their toxicity.
C5	The use of auxiliary substances, such as solvents and additives, should be made unnecessary wherever possible and innocuous when used.
C6	Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized.
C7	Whenever available and practicable, a raw material should be renewable.
C8	Unnecessary derivatization should be minimized or avoided if possible.
C9	Catalytic reagents are superior to stoichiometric reagents.
C10	Chemical products should be designed so that they break down into innocuous degradation products at the end of their function and do not persist in the environment.
C11	Analytical methodologies should be incorporated to allow for real-time monitoring and process control prior to the formation of hazardous substances.
C12	Substances and their applications should be chosen to minimize the potential for chemical accidents.

Similar guidelines were made to define best practices for green engineering in 2003. This compilation of guidelines, known as the San Destin Declaration,<sup>5</sup> exhibits 9 principles of green engineering, focusing on the development of processes in an industrial setting. The 9 principles of green engineering are shown in Table 1.2.

**Table 1.2. 9 Principles of Green Engineering<sup>5</sup>**

E1	Engineer processes and products holistically, use systems analysis, and integrate environmental impact assessment tools.
E2	Conserve and improve natural ecosystems while protecting human health and well-being.
E3	Use life-cycle thinking in all engineering activities.
E4	Ensure that all material and energy inputs and outputs are as inherently safe and benign as possible.
E5	Minimize depletion of natural resources.
E6	Strive to prevent waste.
E7	Develop and apply engineering solutions, while being cognizant of local geography, aspirations, and cultures.
E8	Create engineering solutions beyond current or dominant technologies.
E9	Actively engage communities and stakeholders in development of engineering solutions.

The 12 Principles of Green Chemistry and the 9 Principles of Green Engineering share a few common themes which are fundamental the field of Green Chemistry as a whole:

- Minimization of waste
- Minimize resource depletion/utilize renewables
- Minimize toxicity of materials used
- Minimize exposure of people and environment to toxic materials
- Design processes to avoid hazardous conditions

These concepts, combined with a consideration of economic viability (a result of E9), are what drive the research discussed in this thesis.

Chapter 2 discusses the effect of CO<sub>2</sub> pressure and pH on the Suzuki coupling of basic, nitrogen-containing substrates. This work seeks achieve high reactivity of these substrates without the use of protection/deprotection steps or expensive ligands. Instead, pH and CO<sub>2</sub> are used as adjustable parameters which promote the efficient coupling of basic, nitrogen-containing substrates, helping reduce raw material usage, waste generation, energy use, and material costs.

Chapters 3 and 4 present the development of OATS/Smart Solvent technology useful towards the recovery and re-use of palladium catalysts in Suzuki coupling reactions, thereby minimizing the depletion of palladium feedstocks, reducing the amount of palladium lost to waste streams and the environment, and lowering the cost of operation (solvents and ligands specifically) for a chemical process.

The remainder of this chapter focuses on the background and motivation for the research topics presented in this thesis.

## **1.2 The Effect of CO<sub>2</sub> and pH on the Suzuki Coupling of Basic, Nitrogen-Containing Compounds**

Many pharmaceutical and biologically active molecules contain heterocyclic biaryl moieties. Frequently, these moieties are nitrogen-containing heterocycles such as pyridines.<sup>6-10</sup> The Suzuki coupling reaction, a palladium catalyzed, carbon-carbon coupling of organohalides and organoborons, has emerged as a common step in the synthesis of these types of molecules.<sup>10-13</sup> Both mild reaction conditions and a tolerance towards a variety of functional groups have led to this rise in the popularity of the Suzuki reaction. However, it has been reported that basic, nitrogen-containing substrates, used as building blocks for larger heterocycles with pharmaceutical applications, are generally poor substrates for Suzuki coupling reactions. They react slowly and/or produce low yields of the desired products.<sup>14-18</sup> This is often attributed to coordination of the amine to

palladium decreasing reactivity of the catalyst.<sup>14,19-20</sup> As a result, additional protection/deprotection strategies or expensive, electron-rich ligands must be utilized to achieve reasonable rates and high yields.<sup>14,19,21-22</sup>

Use of protection/deprotection strategies, while common, has its drawbacks. For instance, it requires a minimum of two additional reaction steps. The addition of these steps can drastically lower the efficiency of the synthesis process as well as lead to unwanted side reactions.<sup>23</sup> This strategy also results in an increased waste stream and decreased atom economy, for the solvents and reagents utilized to protect and then deprotect the product, as well as the protecting group itself, are generally discarded. In general, Trost et al. have shown that for every kilogram of fine chemical and pharmaceutical product produced, between 5-100 times that in chemical waste is generated.<sup>24-26</sup>

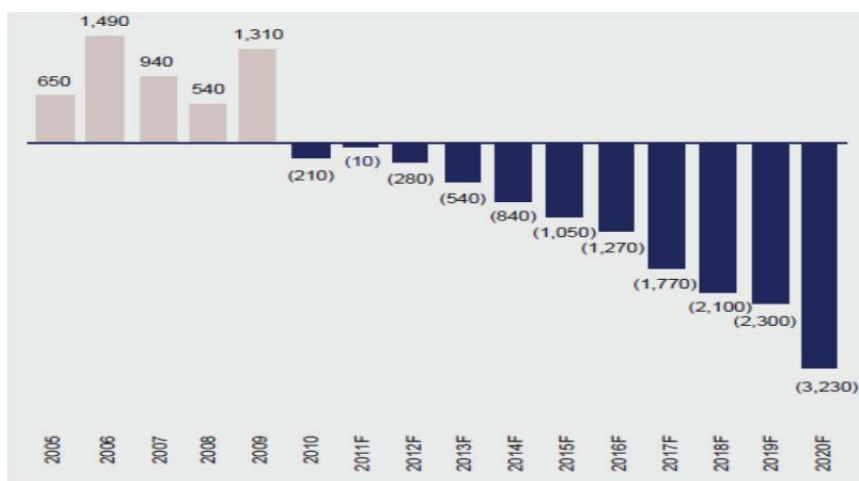
Similarly, the addition of expensive, electron-rich ligands can lead to large cost and/or waste increases due to their high cost and synthesis requirements. Ideally, the recycle of catalyst and ligands would prevent added waste in this technique, however that is one of the challenges of the Suzuki reaction that is still under investigation.<sup>27</sup>

Industrially, it would be desirable to avoid both of these approaches. As an alternative to the typical strategies, Chapter 2 introduces the design of an efficient and simple system for the Suzuki coupling of 4-amino-2-halopyridines in quantitative yields using an inexpensive triphenylphosphine ligand. This system utilizes water content, CO<sub>2</sub> pressure, and/or a manipulation of reaction pH as parameters which can be tuned to allow for efficient Suzuki reaction of a basic pyridine substrate without the use of expensive, electron rich ligands or additional protection/de-protection steps.

### 1.3 Use of Organic-Aqueous Tunable/Smart Solvents to Recover and Recycle

#### Palladium Catalysts

The use of platinum group metals (PGMs) as catalysts has become ubiquitous in the chemical industry and in academia. Metals such as platinum, palladium, rhodium, ruthenium, iridium and osmium have found use in a number of valuable synthetic reactions, including hydrogenation, oxidation, hydroformylation and carbonylation reactions as well as large number of carbon-carbon coupling reactions such as the palladium-catalyzed Suzuki coupling reaction,<sup>28-29</sup> the reaction of interest in this thesis. Unfortunately, PGMs, such as palladium, are not abundant in nature, and, therefore, are relatively expensive. The price of palladium fluctuated between \$20,000 and \$30,000 per kg in 2014.<sup>30</sup> Furthermore, as noted in a 2011 report from Stillwater Mining Company,<sup>31</sup> increased demand for palladium could lead to a shortage in Pd, further increasing the cost of the metal. (Figure 1.1).



**Figure 1.1. Market Deficit of Palladium (in '000s of oz.), forecast to 2020.<sup>31</sup>**

In addition to high and increasing costs, industries are also faced with the challenge of removing palladium from chemical reaction products. Government policies regulate the limits of PGM contamination in order to prevent harm to the public and environment. For instance, the European Agency for the Evaluation of Medicinal Products limits the amount of palladium in pharmaceutical compounds to <10ppm.<sup>32</sup>

The high cost, falling supply, and strict regulations regarding the use of PGMs in chemical processes provide a clear motivation to develop efficient, sustainable technologies to recover and recycle palladium from chemical waste streams. Many existing forms of PGM separation and recycle necessitate the use of expensive ligands or solvents.<sup>33-35</sup> These separations are only made more difficult in the presence of heterocyclic, biaryl compounds (qualities present in certain reaction products) which are known to coordinate with metals and make separation more difficult.

Chapters 3 and 4 propose strategies to separate and recycle palladium catalysts from heterocyclic Suzuki reaction products using Organic-Aqueous Tunable Solvent (OATS)/Smart-solvent technologies in conjunction with the use of additives.<sup>36</sup> OATS technology refers to a solvent system comprised of two miscible liquids (such as acetonitrile and water) that can be made immiscible with the application of an anti-solvent, such as CO<sub>2</sub>. This unique property allows the use of homogeneous reaction (thus higher reaction rate) while retaining the benefits offered by heterogeneous separation (under application of CO<sub>2</sub>).<sup>37</sup> Furthermore, the absorption of CO<sub>2</sub> by OATS solvents is pressure dependent, thus OATS systems exhibit tunability, allowing the system solvent

properties to be easily manipulated as a function of pressure. Finally, OATS constitutes a “green” process in that the additive employed to phase separation is relatively benign CO<sub>2</sub> that is easily removed via depressurization. In this work, the Smart-Solvent technology is similar to OATS, but Toluene is used in the place of CO<sub>2</sub>.

The work shown in Chapter 3 demonstrates a novel technique for the separation and recovery of palladium catalysts from heterocyclic Suzuki reaction products using OATS in combination with a variety of additives. The process allows for the majority of palladium to be removed from post-Suzuki reaction products without the generation of a large waste stream.

Chapter 4 builds upon the work done in Chapter 3. It uses both OATS and Smart-solvent technology (defined here as the use of Toluene in place of CO<sub>2</sub> as anti-solvent) in conjunction with acidic additives to both separate and recycle Pd catalyst following Suzuki coupling reaction of basic, pyridine substrates. This technique represents an effective means of separating and recycling Pd-catalyst from basic, heterocyclic reaction products using inexpensive solvents, additives, and ligands.



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## CHAPTER 2 - EFFECT OF CO<sub>2</sub> AND PH ON THE SUZUKI COUPLING OF BASIC, NITROGEN-CONTAINING COMPOUNDS

### 2.1 Introduction

#### 2.1.1 Overview and Importance of the Suzuki Coupling Reaction

Many pharmaceutical and biologically active molecules are high-value synthetic targets which are heterocyclic and biaryl in nature.<sup>1-5</sup> Coupling reactions which form carbon-carbon bonds, such as the coupling reactions developed by Suzuki-Miyaura, Stille, and others, are often a critical step in the synthesis of biaryl, heterocyclic molecules. The Suzuki-Miyaura reaction, a Pd-catalyzed coupling of an organic boronic acid/ester with an organic halide (Figure 2.1) that requires the use of a base,<sup>6-8</sup> has emerged as a widely used method of forming C-C bonds between aryl moieties in industry and academia. Gleevec<sup>TM</sup> (Figure 2.2), a pharmaceutical drug, is an example of a heterocyclic biaryl compound whose synthesis uses Suzuki coupling to form a carbon-carbon bond (in blue).

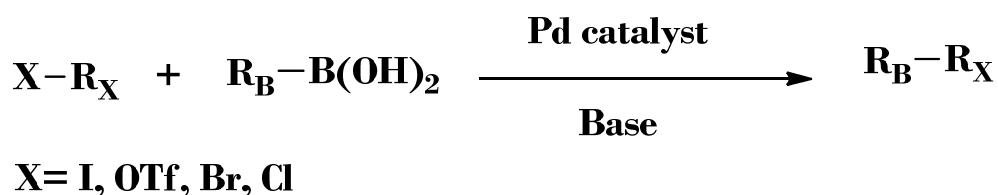
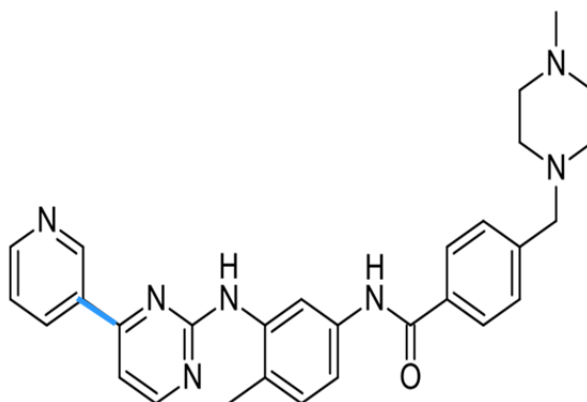


Figure 2.1. Generalized Suzuki coupling reaction.



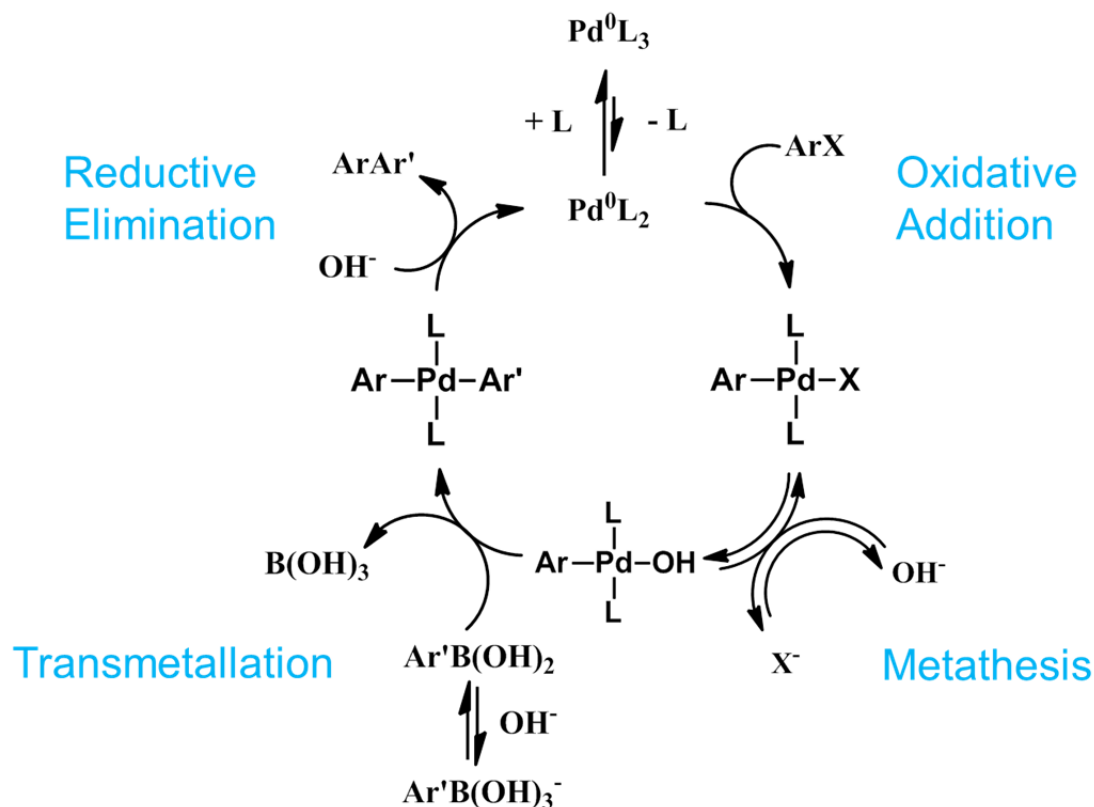
**Figure 2.2. Gleevac™**

The Suzuki reaction's popularity partly stems from its versatility, for it is, applicable to reaction of a wide variety of alkenyl, aryl and alkynyl halide and triflate substrates.<sup>6,9</sup> Additionally, its versatility is demonstrated by its applicability to a variety of organoboranes. Boronic acids, esters, trialkylboranes, and other organoboranes can all be utilized in the reaction, though boronic acids are the most common due to their stability, availability, price and low toxicity.<sup>8,10</sup> Furthermore, The reaction is tolerant of a broad range of functional groups including esters, alcohols, amines and nitro groups; it also displays high stereo- and regio-selectivity. Additionally, the reaction is generally able to proceed under relatively mild reaction conditions and often does not require the use of expensive solvents.<sup>11-12</sup>

### 2.1.2 Mechanism of the Suzuki Reaction

A general mechanism of the Suzuki coupling, as outlined by Amatore, is displayed in Figure 2.3.<sup>13</sup> The active form of the palladium catalyst in the catalytic cycle is believed to be  $\text{Pd}^0$ , with anywhere from one to three ligands, depending on the ligand

size and shape.<sup>10,14</sup> The catalytic cycle begins with oxidative insertion of the  $\text{Pd}^0$  into the carbon-halide bond of the aryl halide (Oxidative Addition), resulting in a  $\text{Pd}^{\text{II}}$  species. Base, such as hydroxide, (in aqueous systems) then exchanges for the halide (Metathesis). Transmetalation then occurs through the transfer of the aryl species from the arylboronic acid to the palladium, followed by reductive elimination forming the reaction product and regenerating of the active catalyst. The initial and final steps (oxidative addition and reductive elimination) are relatively well supported and accepted as outlined below.<sup>8,15-17</sup> However, there is some disagreement regarding the details of the metathesis and transmetalation steps.

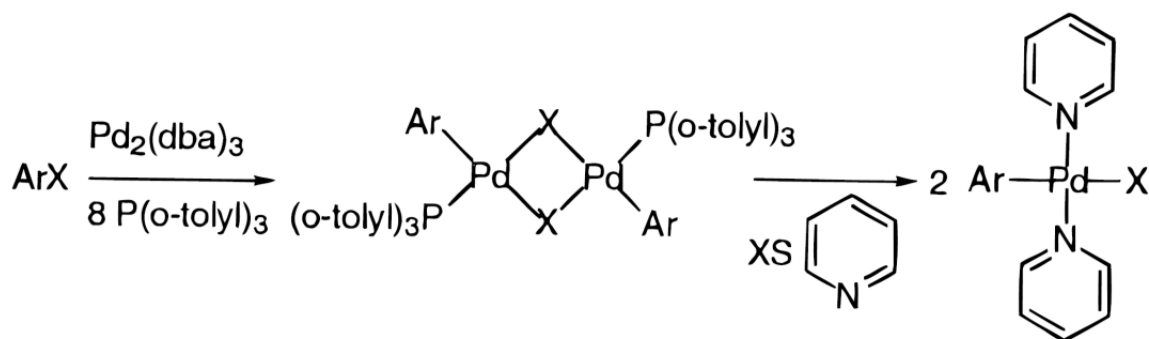


**Figure 2.3. Suzuki coupling mechanism.**

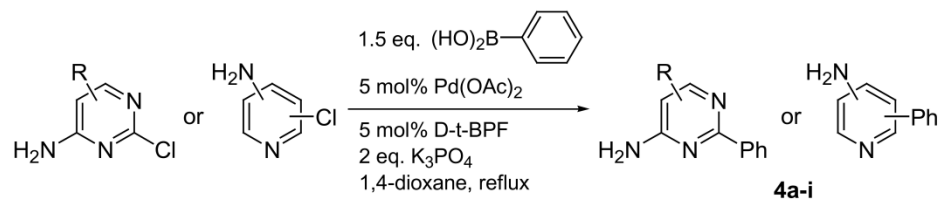
### 2.1.3 Challenges of the Suzuki Reaction

While The Suzuki reaction has many advantages, a variety of challenges also exist. One challenge lies in the relative reactivity of organohalides. The general order of reactivity for organohalides is generally thought to be  $I > Br \gg Cl$  with iodo compounds being most reactive.<sup>6</sup> While less reactive, chlorinated substrates are desirable from an industrial standpoint, for they are often cheaper than the corresponding bromo- and iodo-substrates. Additionally, they are readily available, and the weight of the byproducts would be less than the bromo- and iodo- substrates.

Another challenge of the Suzuki coupling reaction is the efficient coupling of basic, nitrogen containing substrates. These nitrogen centers can coordinate with the catalyst and prevent it from entering the catalytic cycle, thus resulting in poor reaction yields.<sup>18-21</sup> Figure 2.4 and Figure 2.5 show examples of this coordination and poor reaction yields of more basic substrates. The poor reactivity demonstrated by these basic, heterocyclic substrates is significant, for, as seen with Gleevac<sup>TM</sup>, many high value targets contain these moieties which must be coupled.<sup>22</sup>



**Figure 2.4. Formation of bis (aminopyridine) palladium complexes which are less reactive towards cross-coupling reactions.**



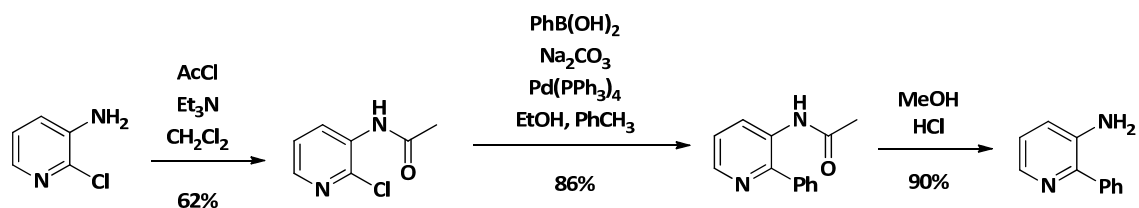
Substrates	Products	% Yield
 $pK_a$ 1.6		<b>4e</b> 93
 $pK_a$ 2.1		<b>4f</b> 82
 $pK_a$ 2.8		<b>4g</b> 68
 $pK_a$ 4.5		<b>4h</b> 72
 $pK_a$ 4.8		<b>4i</b> 30

**Figure 2.5. Yields and conjugate acid  $pK_a$  of the coupling of various aminochloropyridines with phenylboronic acid.<sup>21</sup>**

One strategy to overcome the limitation presented by basic reaction substrates is protection/deprotection of the amine functionality. Caron et al. demonstrated that the reaction of 3-amino-2-chloropyridine with phenylboronic acid in the presence of

palladium tetrakis(triphenylphosphine) and sodium carbonate yields no sign of the desired product.<sup>18</sup> However, protection of the amine with an acyl moiety and then reaction under the same conditions proceeded in 86% yield of the desired biaryl, nitrogen containing product (Figure 2.6). The overall yield for the three steps, however, is only 48%.

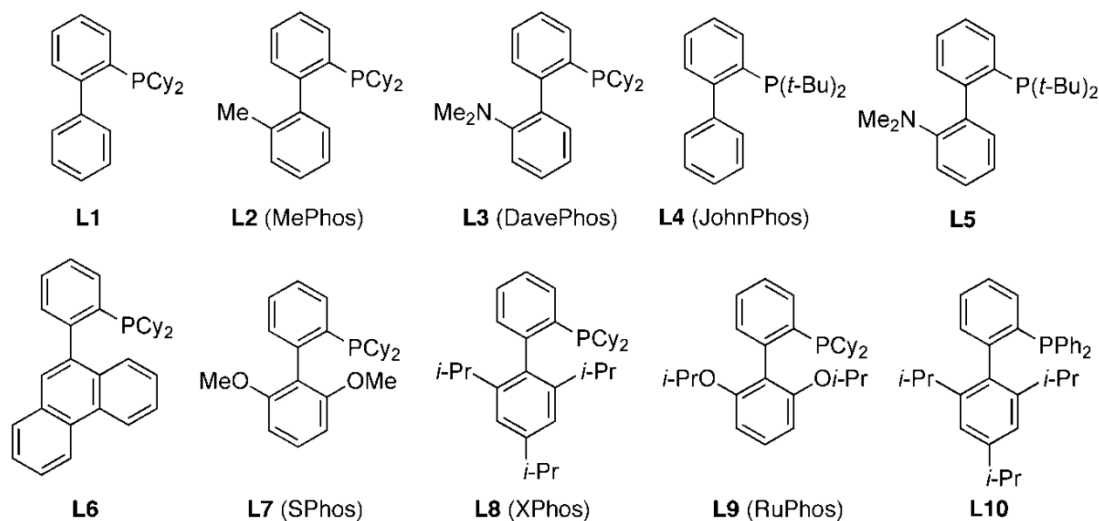
The downside of this strategy is the increased number of steps necessary to achieve the desired product. Extra steps mean more energy and time is necessary, and more waste is produced. Additionally, as Figure 2.6 shows, these additional steps can also result in lower overall yields of the product.



**Figure 2.6. Acetyl protection of 3-amino-2-chloropyridine to promote reaction in Suzuki coupling.<sup>18</sup>**

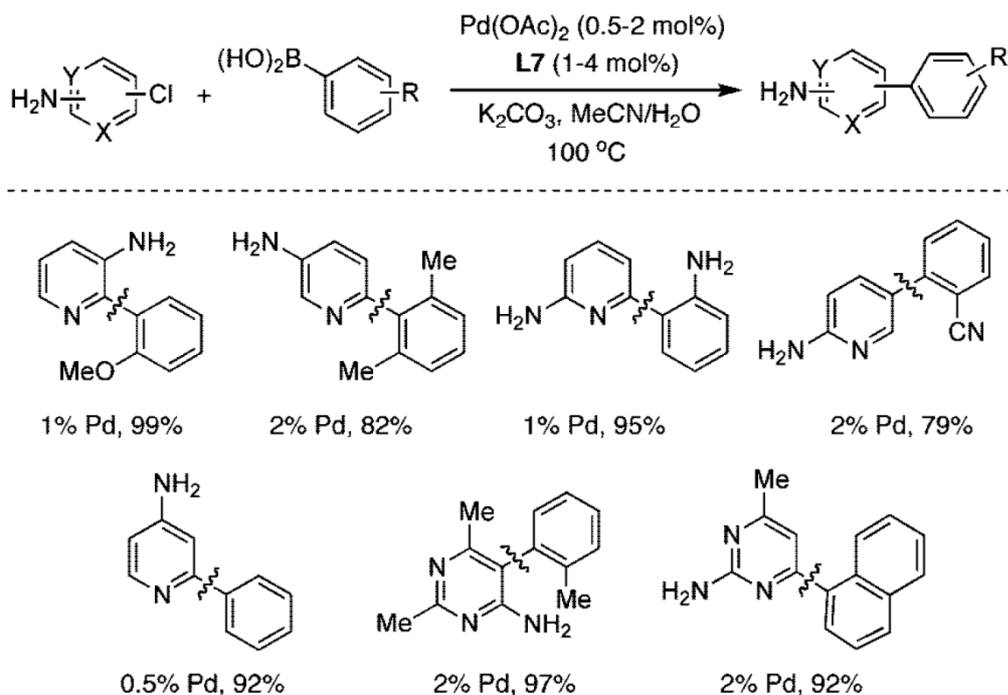
Another strategy to increase the reactivity of basic amines is the use of electron-rich ligands. The Buchwald group developed a series of novel ligands to promote the couplings of chloro-containing substrates (Figure 2.7). These ligands utilize di-alkyl groups on the phosphorus to increase electron density on the phosphorus and increase the rate of oxidative addition, while the size of the alkyl groups increases the rate of reductive elimination.





**Figure 2.7. Dialkylbiaryl ligands developed by Buchwald to promote reactions of chlorinated substrates.<sup>10</sup>**

These bulky ligands have been shown to prevent coordination of amines to the palladium center.<sup>22-23</sup> SPhos (L7, Figure 2.7), specifically, was shown to facilitate the cross-coupling of a variety of aminochloropyridines with phenyl boronic acids to provide the products in high yields (Figure 2.8). The downside of ligands such as Buchwald's ligands is that they are often either very expensive or not commercially available.<sup>24</sup>

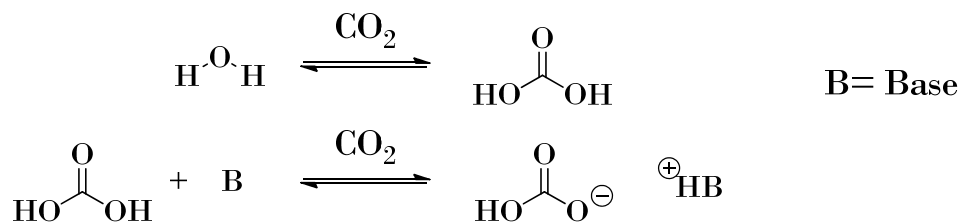


**Figure 2.8. Efficient coupling of aminochloropyridines utilizing ligand SPhos.**

From an industrial point of view, it would be desirable to avoid both the addition of protection/deprotection steps and the use of expensive ligands. A potential strategy would be to run Suzuki in the presence of  $\text{CO}_2$ .

$\text{CO}_2$  is known to react with primary and secondary amines under certain conditions to form ammonium carbamate species.<sup>25-27</sup> Originally, the goal of this work was to run reactions under  $\text{CO}_2$  pressure and use the formation of the carbamate species as an in-situ method of amine protection. However, it was also recognized that the application of  $\text{CO}_2$  could have other effects on the system.  $\text{CO}_2$  is also known to react with water to form carbonic acid, which can then react with base to produce new phosphate and bicarbonate species (Figure 2.9). This change in base system can also result in a change of the effective pH at which reaction is occurring. Additionally, the application of  $\text{CO}_2$  pressure would lead to absorption of the  $\text{CO}_2$  in certain solvents,<sup>28</sup> thus affecting the phase behavior of the solvent system. As a result, all of these factors

must be considered when determining the effect of CO<sub>2</sub> pressure on the Suzuki coupling of amine-containing substrates.



**Figure 2.9. Reaction of CO<sub>2</sub> with water and base to form new aqueous phase composition.**

This chapter describes the effect of CO<sub>2</sub> pressure and pH on the Pd-triphenylphosphine catalyzed Suzuki coupling of 4-amino-2-halopyridines and 2-halopyridines with phenylboronic acid employing potassium phosphate in acetonitrile-water at 70°C. The yields of the reactions under CO<sub>2</sub> and nitrogen (N<sub>2</sub>) are compared, along with the relevant rate profiles for each reaction. Additionally, the yields of the coupled products as a function of pH are reported and discussed.

## 2.2 Experimental

### 2.2.1 Materials

All chemicals were purchased from Sigma-Aldrich, Matrix or VWR and used as received unless otherwise noted. All chemicals were stored under inert dry atmosphere. The CO<sub>2</sub> employed was SFC grade from Airgas, certified to contain less than < 250 ppb H<sub>2</sub>O with a purity of 99.9999%.

### 2.2.2 Experimental Procedure

#### 2.2.2.1 *Procedures for 4-Amino-2-halopyridine*

*Reaction of 4-amino-2-halopyridine with phenylboronic acid under a nitrogen atmosphere.*

4-Amino-2-chloropyridine (2.057 g, 16 mmol, 1 eq.) or 4-amino-2-bromopyridine (2.768 g, 16 mmol, 1 eq.), phenylboronic acid (2.536 g, 1.3 eq.), K<sub>3</sub>PO<sub>4</sub> (10.189 g, 3 eq.), and Pd (TPP)<sub>2</sub>Cl<sub>2</sub> (0.562 g, 5 mol%) were added to a 100 mL three-neck Morton flask. The flask was evacuated and backfilled with nitrogen. Degassed acetonitrile (30 mL) and degassed water (10 mL for 25% v/v reactions; 20 mL for 40% v/v reactions) were added by means of an air-tight syringe. The reaction vessel was insulated with glass wool and heated to reflux at 70°C (monitored by internal thermometer) with magnetic stirring under an atmosphere of N<sub>2</sub> for 24 h. The initial reaction time (t = 0) was taken when the reaction mixture reached an internal temperature of 70°C; this took approximately 10-15 minutes. The reactions were biphasic with two liquid phases.

*Reaction of 4-amino-2-halopyridine with phenylboronic acid under varying pressures of carbon dioxide.*

4-Amino-2-chloropyridine (2.057 g, 16 mmol, 1 eq.) or 4-amino-2-bromopyridine (2.768 g, 16 mmol, 1 eq.), phenylboronic acid (2.536 g, 1.3 eq.),  $K_3PO_4$  (10.189 g, 3 eq.), and  $Pd(TPP)_2Cl_2$  (0.562 g, 5 mol%) were added to a 300 mL stainless steel bomb (Parr reactor). The Parr reactor was then purged with a flow of  $CO_2$  for 15 minutes. Degassed acetonitrile (30 mL) and degassed water (10 mL for 25% v/v reactions; 20 mL for 40% v/v reactions) were then added by means of an air-tight syringe. The Parr reactor was then pressurized with  $CO_2$  via a model 260D or 500D ISCO syringe pump to within ~6.8 atm. of the desired pressure. The reaction mixture was mechanically stirred by means of a built-in impeller at a stirring rate of 415 rpm and heated to 70°C as monitored by an internal thermocouple. The pressure of  $CO_2$  was then increased to the desired pressure. The initial reaction time ( $t = 0$ ) was taken when the reaction mixture reached an internal temperature of 70°C and the final  $CO_2$  pressure has been reached; this took approximately 10 minutes. Constant pressure was maintained throughout the reaction by the ISCO pump. The reaction mixture was heated for 24 h. The reactions are biphasic with two liquid phases.

#### *Workup Procedure*

After reacting for 24 h the reaction vessel was cooled to room temperature. Depressurization was necessary for the reactions conducted under an atmosphere of  $CO_2$ . Methanol was added (~100 mL) to the reaction mixture which resulted in the precipitation of a solid. At this point the reaction mixture is characterized by two phases- a solid phase and a single liquid phase. The mixture was filtered and the filtrate analyzed by gas chromatography/flame ionization detector (GC-FID) using a Shimadzu GC-2010 gas chromatograph fitted with a Supelco PTA-5 (30m x 0.32 mm x 1.00  $\mu m$ , length x inside diameter x film thickness) capillary column. Product yields were calculated using the calibration curves discussed below. The filtrate was then transferred to a round bottom flask and the solvent removed *in vacuo*. The crude product was analyzed by  $^1H$ -

NMR ( $\text{CDCl}_3$ ) using a 300 MHz Varian NMR spectrometer and compared to standards to determine NMR yields (refer to section VI for example and calculation).

*Reaction of 2-halo-4-aminopyridine with phenylboronic acid as a function of time.*

To monitor reactions as a function of time, samples were taken from the organic layer for analysis by GC-FID.

*Reactions under Atmospheric Nitrogen*

For reactions conducted under a nitrogen atmosphere the stirring was stopped briefly at specified times in order to allow the acetonitrile and water phases to separate. Air tight syringes were used to remove 0.2 mL samples from the organic phase; stirring was then resumed. The 0.2 mL sample was placed in a vial from which 0.1 mL was transferred to a GC vial by means of an Eppendorf calibrated pipette. Methanol (0.9 mL) was then added to the GC vial by an Eppendorf pipette and the sample analyzed by GC-FID.

*Reactions under  $\text{CO}_2$  Pressure*

For reactions conducted under  $\text{CO}_2$  pressures, samples were removed through a stainless steel dip tube which extends into the organic phase. Stirring was stopped briefly to allow the acetonitrile and water phases to separate. The valve was opened so that the pressure differential slowly drove the sample out of the reactor into a vial in the form of droplets. After  $\sim 0.2$  mL was collected the valve was shut and stirring resumed. Then 0.1 mL of the sample was transferred from the vial to a GC vial by means of an Eppendorf pipette. Methanol (0.9 mL) was added to the GC vial by an Eppendorf pipette and the sample was analyzed by GC-FID.

*2.2.2.2 Experimental procedures for 2-halopyridines.*

*Reaction of 2-halopyridine with phenylboronic acid under a nitrogen atmosphere.*

Phenylboronic acid (2.536 g, 1.3 eq.),  $K_3PO_4$  (10.189 g, 3 eq.), and  $Pd(TPP)_2Cl_2$  (0.562 g, 5 mol%) were added to a 100 mL three-neck Morton flask. The flask was evacuated and backfilled with nitrogen. 2-Chloropyridine (1.817 g, 16 mmol, 1 eq.) or 2-bromopyridine (2.528 g, 16 mmol, 1 eq.), followed by degassed acetonitrile (30 mL) and then degassed water (10 mL for 25% v/v reactions; 20 mL for 40% v/v reactions) were added by means of an air-tight syringe. The reaction vessel was insulated with glass wool and heated to reflux at 70°C (monitored by internal thermometer) with magnetic stirring under an atmosphere of  $N_2$  for 24 h. The initial reaction time ( $t = 0$ ) was taken when the reaction mixture reached an internal temperature of 70°C; this took approximately 10-15 minutes. The reactions were biphasic with two liquid phases.

*Reaction of 2-halopyridine with phenylboronic acid under varying pressures of carbon dioxide.*

Phenylboronic acid (2.536 g, 1.3 eq.),  $K_3PO_4$  (10.189 g, 3 eq.), and  $Pd(TPP)_2Cl_2$  (0.562 g, 5 mol%) were added to a 300 mL stainless steel bomb (Parr reactor). The Parr reactor was then purged with a flow of  $CO_2$  for 15 minutes. 2-Chloropyridine (1.817 g, 16 mmol, 1 eq.) or 4-amino-2-bromopyridine (2.528 g, 16 mmol, 1 eq.) followed by degassed acetonitrile (30 mL) and then degassed water (10 mL for 25% v/v reactions; 20 mL for 40% v/v reactions) were then added by means of an air-tight syringe. The Parr reactor was then pressurized with  $CO_2$  via a model 260D or 500D ISCO syringe pump to within ~6.8 atm. of the desired pressure. The reaction mixture was mechanically stirred by means of a built-in impeller at a stirring rate of 415 rpm and heated to 70°C as monitored by an internal thermocouple. The pressure of  $CO_2$  was then increased to the desired pressure. The initial reaction time ( $t = 0$ ) was taken when the reaction mixture reached an internal temperature of 70°C and the final  $CO_2$  pressure has been reached; this

took approximately 10 minutes. Constant pressure was maintained throughout the reaction by the ISCO pump. The reaction mixture was heated for 24 h. The reactions are biphasic with two liquid phases.

#### *Workup Procedure*

Workup was conducted in the same manner as described above for the 4-amino-2-halopyridines.

#### *Reaction of 2-halopyridine with phenylboronic acid as a function of time.*

Sampling was conducted in the same manner as described above for the 4-amino-2-halopyridines.

#### *2.2.2.3 Isolation of 4-Amino-2-phenylpyridine from the reaction of 4-amino-2-bromopyridine with phenylboronic acid under CO<sub>2</sub> pressure.*

4-Amino-2-bromopyridine (2.761 g, 15.96 mmol, 1 eq.), phenylboronic acid (2.536 g, 1.3 eq.), K<sub>3</sub>PO<sub>4</sub> (10.189 g, 3 eq.), and Pd(TPP)<sub>2</sub>Cl<sub>2</sub> (0.562 g, 5 mol%) were added to a 300 mL stainless steel bomb (Parr reactor). The Parr was then purged with a flow of CO<sub>2</sub> for 15 minutes. Degassed acetonitrile (30 mL) and degassed water (20 mL) were then added by air-tight syringe. The Parr was then pressurized with CO<sub>2</sub> by means of a model 500D ISCO syringe pump to ~24 atm. CO<sub>2</sub>. The reaction mixture was mechanically stirred by means of a built-in impeller at a stirring rate of 415 rpm and heated to 70°C as monitored by an internal thermocouple. The pressure was then increased to 30.6 atm. CO<sub>2</sub>. The initial reaction time (t = 0) was taken when the reaction mixture reached an internal temperature of 70°C and the final CO<sub>2</sub> pressure has been reached; this took approximately 10 minutes. Constant pressure was maintained throughout the reaction by the ISCO pump. The reaction mixture was heated for 24 h.



After 24 h the Parr reactor was cooled to room temperature and depressurized. Methanol was added (~100 mL) to the reaction mixture which resulted in the precipitation of a solid. At this point the reaction mixture is characterized by two phases- a solid phase and a single liquid phase. The mixture was filtered and the filtrate analyzed by GC-FID using a Shimadzu GC-2010 gas chromatograph fitted with a Supelco PTA-5 (30m x 0.32 mm x 1.00  $\mu$ m, length x inside diameter x film thickness) capillary column. Using the above described calibration curves, the yield of 2-phenyl-4-aminopyridine was calculated to be 99%; the conversion was 100%. The filtrate was transferred to a round bottom flask and the solvent was removed *in vacuo* leaving a brown solid. The crude mixture was loaded onto neutral silica (~10 g) then added to a column packed with neutral silica (pH~7). A hexanes/ethyl acetate (EtOAc) gradient was used. Biphenyl was removed first under 100% hexanes. The EtOAc concentration was gradually increased to 50% and then held at 50% until the product had completely eluted from the column as indicated by TLC. The product fractions were combined and the solvent removed *in vacuo* to yield 94% 4-amino-2-phenylpyridine as yellow crystalline solid (2.54 g, 14.992 mmol).  $^1\text{H}$  and  $^{13}\text{C}$  NMR of the pure product are shown below (Figure 2.10 and Figure 2.11).

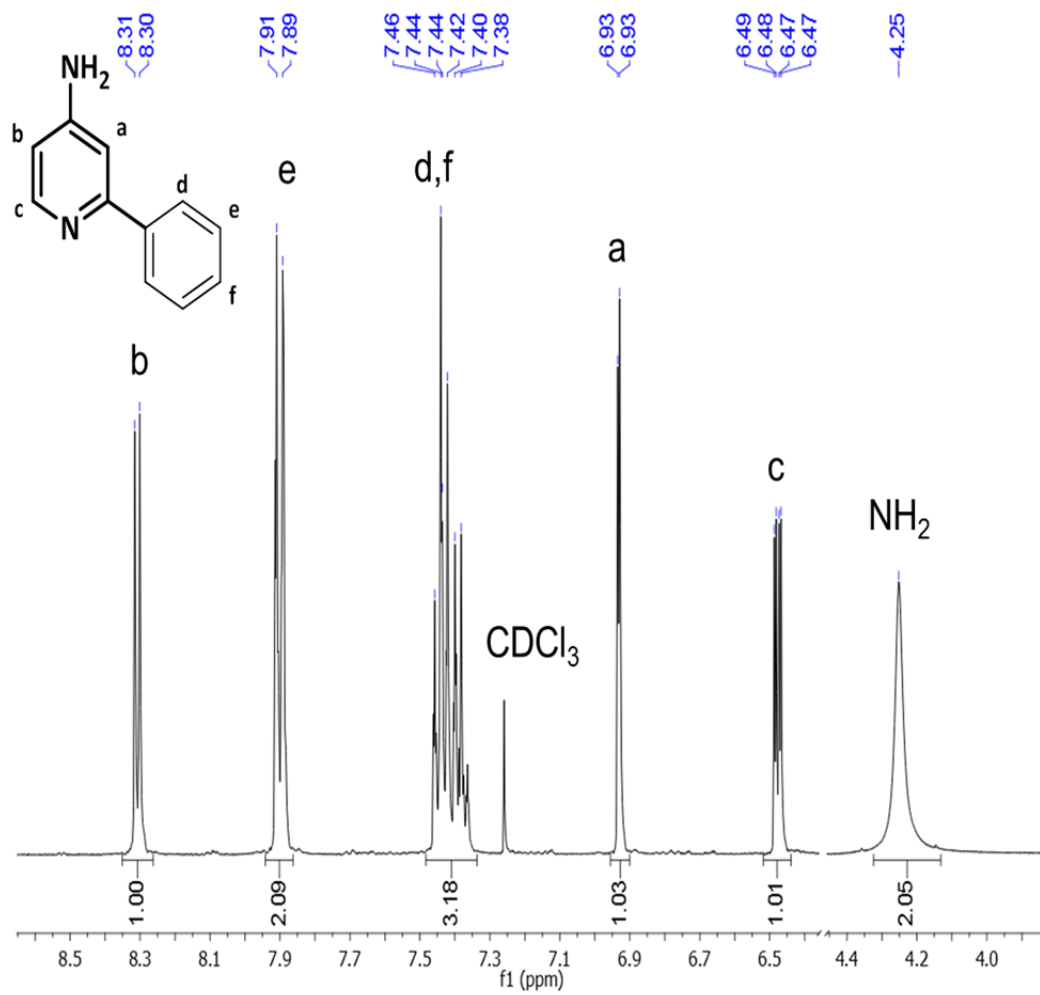
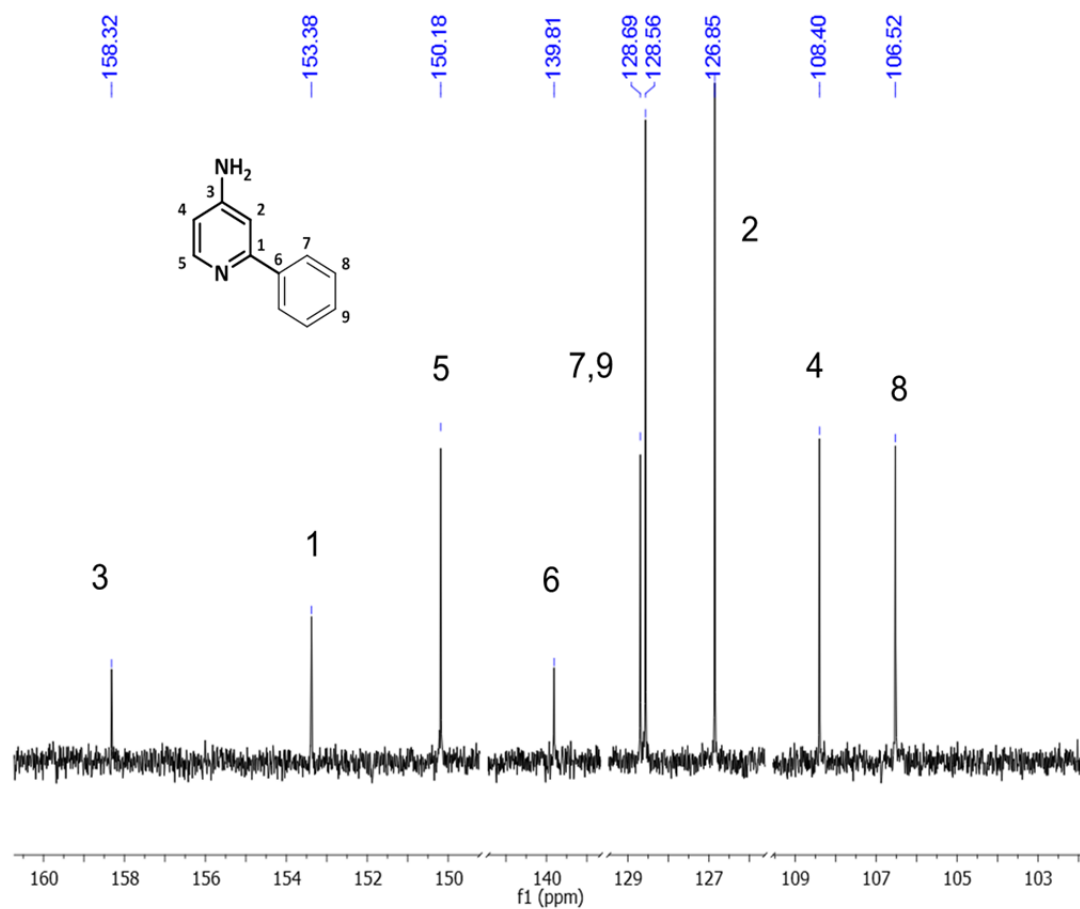


Figure 2.10.  $^1\text{H}$  NMR of 2-phenyl-4-aminopyridine.



**Figure 2.11.** <sup>13</sup>C NMR of 4-amino-2-phenylpyridine.

#### 2.2.2.4 Composition of Buffered Phases for pH vs. Yield

The following tables detail which base(s), the equivalents of the base (relative to the substrate), the pH before and after reaction, and the yields for each reaction used for the study of pH's effect on yield.

**Table 2.1. Buffer compositions for 4-amino-2-bromopyridine at 40% water.**  
**\*Reagents and solvents were preconditioned with CO<sub>2</sub> then purged and run under N<sub>2</sub>.**

<b>4-NH<sub>2</sub>-2-BrPyr, 40% H<sub>2</sub>O</b>			
<b>Base (equiv.)</b>	<b>Yield (%)</b>	<b>pH before</b>	<b>pH after</b>
K <sub>3</sub> PO <sub>4</sub> (3)	23±4	13	13
K <sub>4</sub> P <sub>2</sub> O <sub>7</sub> (3)	50±1	10.58	9.67
K <sub>2</sub> HPO <sub>4</sub> /KHCO <sub>3</sub> (1/2)	79±3	9.2	8.8
K <sub>2</sub> HPO <sub>4</sub> /KHCO <sub>3</sub> (3/3)	51±3	9.64	9.6
K <sub>2</sub> HPO <sub>4</sub> (3)	90±2	9.5	7.95
K <sub>3</sub> PO <sub>4</sub> , 30 psi CO <sub>2</sub> (3)	83±0	N/A	7.7
K <sub>3</sub> PO <sub>4</sub> , 100 psi CO <sub>2</sub> (3)	91±8	N/A	7.9
K <sub>2</sub> HPO <sub>4</sub> /KHCO <sub>3</sub> /KH <sub>2</sub> PO <sub>4</sub> (2.4/3.5/0.6)	51±4	8.4	9.85
precond. K <sub>3</sub> PO <sub>4</sub> * (3)	76±6	8	8.3
pre-cond. SM. and K <sub>3</sub> PO <sub>4</sub> * (3)	75±2	7.9	8.1
CsF (3)	95±4	8.97	8.1

**Table 2.2. Buffer compositions for 4-amino-2-bromopyridine at 25% water.**

<b>4-NH<sub>2</sub>-2-BrPyr, 25% H<sub>2</sub>O</b>		
<b>Base (equiv.)</b>	<b>Yield (%)</b>	<b>pH after</b>
KH <sub>2</sub> PO <sub>4</sub> (3)	3	5.9
K <sub>3</sub> PO <sub>4</sub> (3)	17±3	13
K <sub>2</sub> HPO <sub>4</sub> /K <sub>2</sub> CO <sub>3</sub> (3/3)	23	11.3
K <sub>4</sub> P <sub>2</sub> O <sub>7</sub> (3)	26±4	10.6
K <sub>2</sub> HPO <sub>4</sub> /KHCO <sub>3</sub> (1/2)	35±1	9.2
K <sub>2</sub> HPO <sub>4</sub> /KHCO <sub>3</sub> (3/3)	41±3	10.3
K <sub>2</sub> HPO <sub>4</sub> (3)	41±8	9.8

**Table 2.3. Buffer compositions for 2-bromopyridine at 40% water**

<b>2-BrPyr, 40% H<sub>2</sub>O</b>			
<b>Base (equiv.)</b>	<b>Yield</b>	<b>Initial pH</b>	<b>final pH</b>
K <sub>3</sub> PO <sub>4</sub> (3)	92±5	12.8±0.3	11.6±0.5

K <sub>3</sub> PO <sub>4</sub> , 450 psi CO <sub>2</sub> (3)	15±0.3	12.8±0.3	7.8±0.5
K <sub>2</sub> HPO <sub>4</sub> (3)	26±2	9.4±0.1	8.4±0.3
K <sub>2</sub> HPO <sub>4</sub> /KHCO <sub>3</sub> (1/2)	36±8	9.2±0.1	9.6±0.3
KH <sub>2</sub> PO <sub>4</sub> (3)	23±4	5.2±0.0	3.4±0.1
K <sub>2</sub> CO <sub>3</sub> (3)	66±1	11.9±0.1	10.5±0.2
KHCO <sub>3</sub> (3)	64±5	8.9±0.1	9.6±0.3
K <sub>2</sub> HPO <sub>4</sub> /KHCO <sub>3</sub> /KH <sub>2</sub> PO <sub>4</sub> (2.4/3.5/0.6)	25±2	8.5±0.1	9.2±0.1
CsF (3)	29±7	N/A	8.6±0.2
KOH (3)	69±6	14.75±0.07	11.7±0.0

**Table 2.4. Buffer compositions for 4-amino-2-chloropyridine at 40% water**

<b>4-NH<sub>2</sub>-2-ClPyr, 40% H<sub>2</sub>O</b>				
<b>Base (equiv.)</b>	<b>yield</b>	<b>st. dev</b>	<b>pH before</b>	<b>pH after</b>
K <sub>3</sub> PO <sub>4</sub>	30±2	2	N/A	12.635
K <sub>2</sub> HPO <sub>4</sub>	64±2	2	9.5	8.2

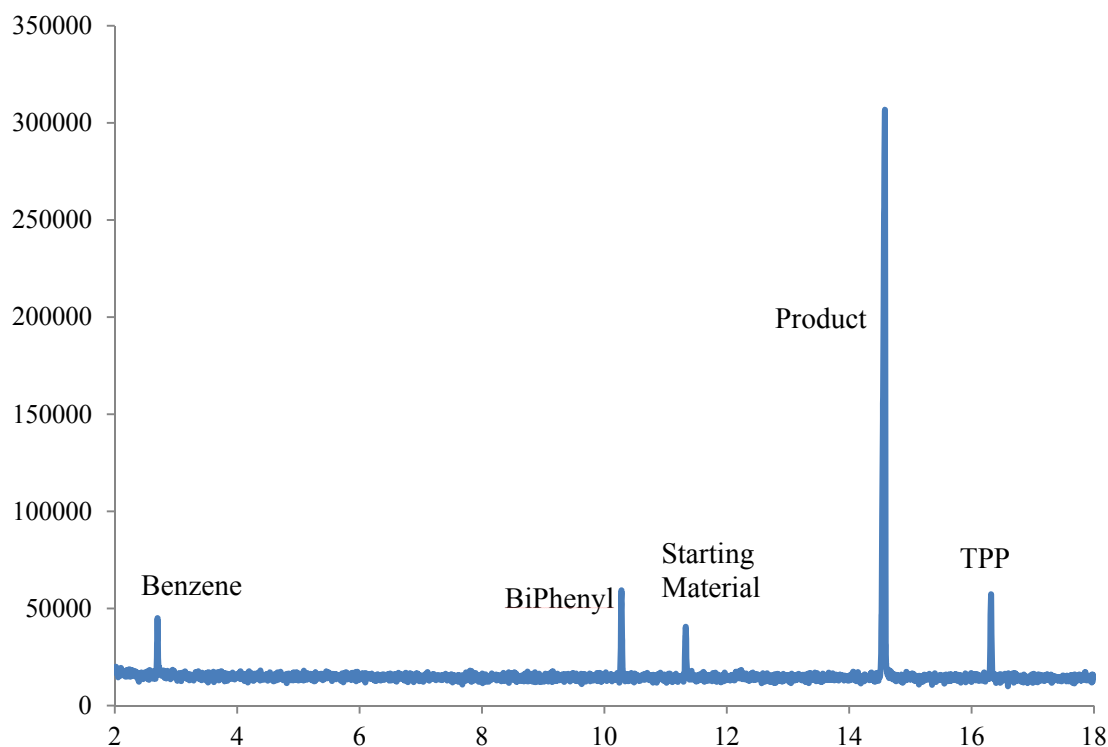
30 psi CO <sub>2</sub>	93±3	3	N/A	7.95
100 psi CO <sub>2</sub>	98±3	3	N/A	7.625

**Table 2.5. Buffer compositions for 2-chloropyridine at 40% water**

<b>2-ClPyr, 40% H<sub>2</sub>O</b>			
<b>Base (equiv.)</b>	<b>Yield</b>	<b>Initial pH</b>	<b>final pH</b>
K <sub>3</sub> PO <sub>4</sub> (3)	79±1	13.2±0.1	11.6±0.1
K <sub>3</sub> PO <sub>4</sub> , 450 psi CO <sub>2</sub> (3)	32±6	13.2±0.1	7.6±0.1
K <sub>2</sub> HPO <sub>4</sub> (3)	42±9	9.3±0.1	8.3±0.1
K <sub>2</sub> CO <sub>3</sub> (3)	94±2	11.7±0.1	10.5±0.0

### 2.2.3 Analyses

#### 2.2.3.1 *GC-FID Chromatograms and Calibration Curves*

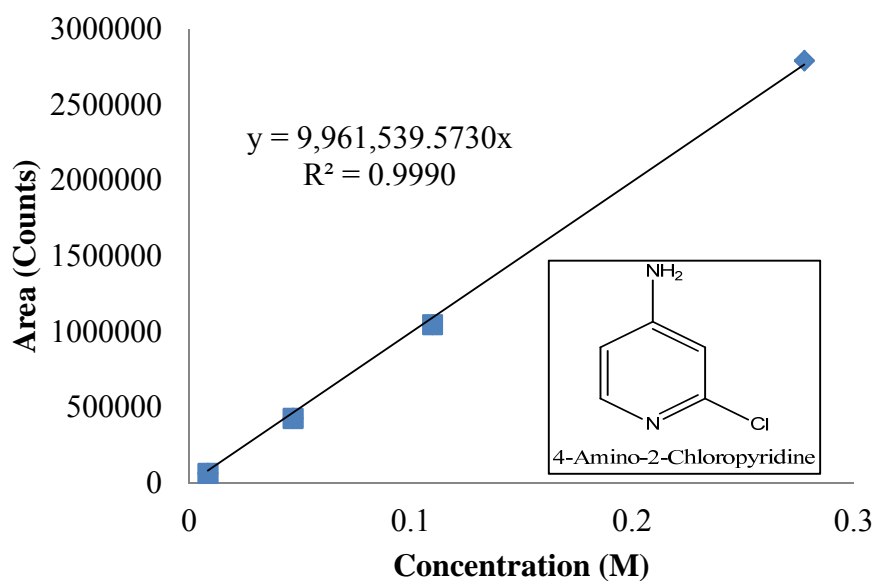


**Figure 2.12. Example GC-FID spectra: reaction of 4-amino-2-bromopyridine with phenylboronic acid under 2 atm. CO<sub>2</sub> and 40% water after 24 h after workup. Calibration curves are used to relate the area of each peak to a concentration, which is then used to calculate yield and conversion.**

Calibration curves were created from pure substrate and product standards. Stock solutions (1 M) were made using a 75/15/10 mixture of methanol/acetonitrile/water to mimic the solvent system of the reaction systems after workup. Multiple samples of concentrations between 0.01 M and 0.5 M were then made from dilution of the stock solution with the same solvent mixture and analyzed by GC-FID. Plots of concentration versus area were created for each compound using Microsoft Excel and a trend line analysis used to provide the calibration curve and confirm the plot followed a straight line. Calibration curves for 4-amino-2-chloropyridine, 4-amino-2-bromopyridine, and 2-



bromopyridin-4-ylamine are displayed in Figure 2.13, Figure 2.14, and Figure 2.15. Calibration curves for 2-chloropyridine, 2-bromopyridine and 2-phenylpyridine are displayed in Figure 2.16, Figure 2.17, and Figure 2.18.



**Figure 2.13. GC-FID calibration curve of 4-amino-2-chloropyridine.**

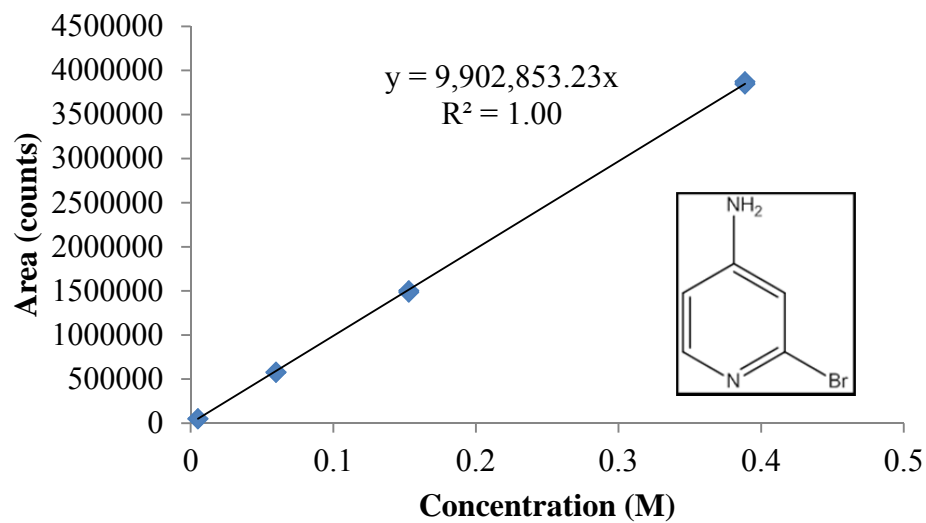


Figure 2.14. GC-FID Calibration Curve for 4-amino-2-bromopyridine.

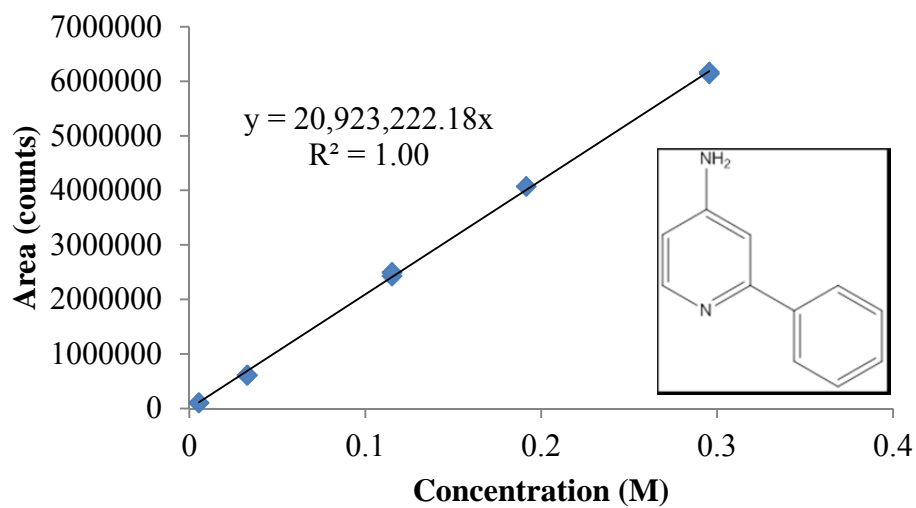


Figure 2.15. GC-FID Calibration Curve for 2-phenylpyridine-4-ylamine.

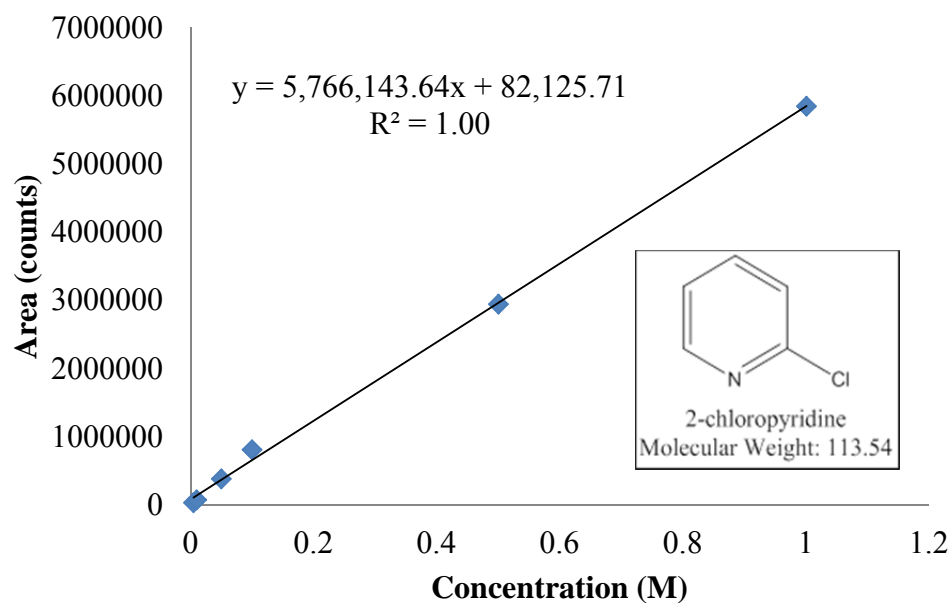


Figure 2.16. GC-FID Calibration Curve for 2-chloropyridine.

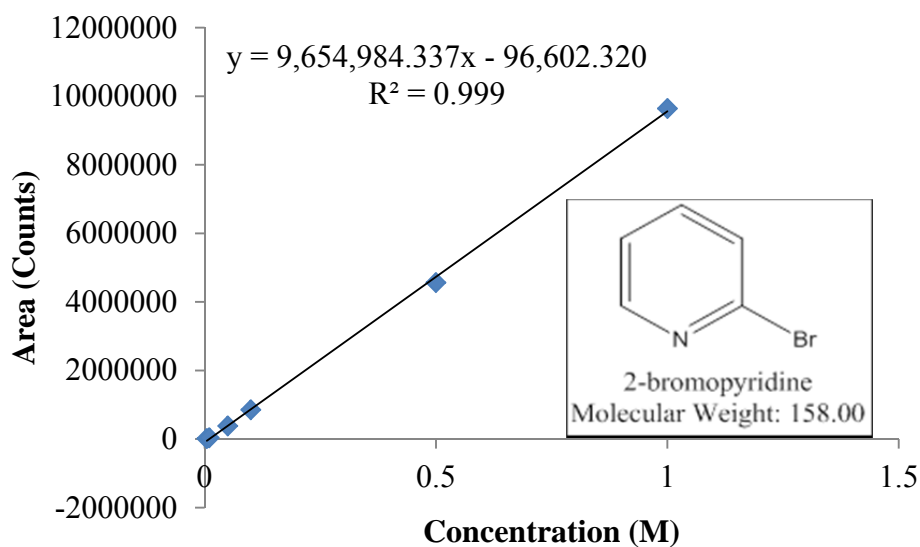
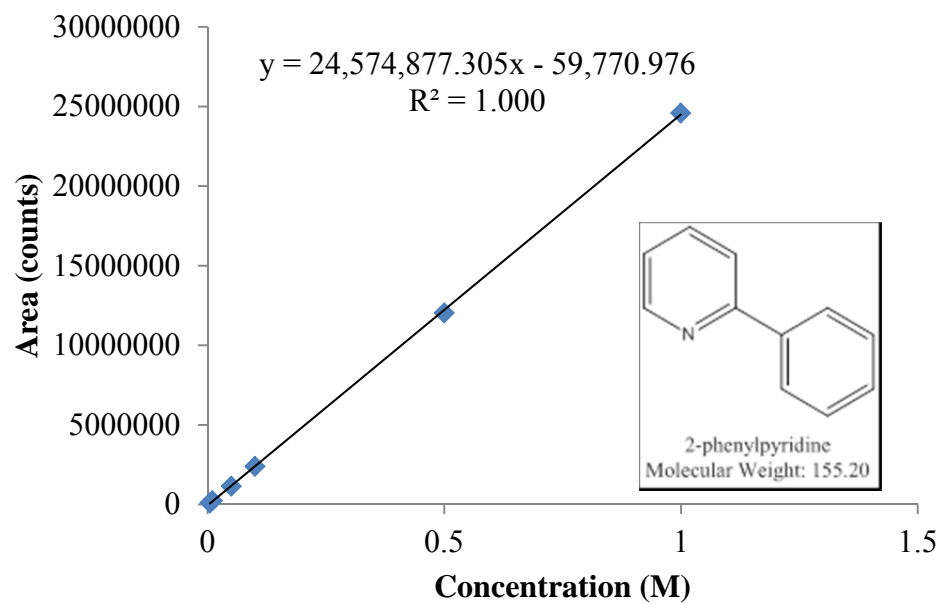


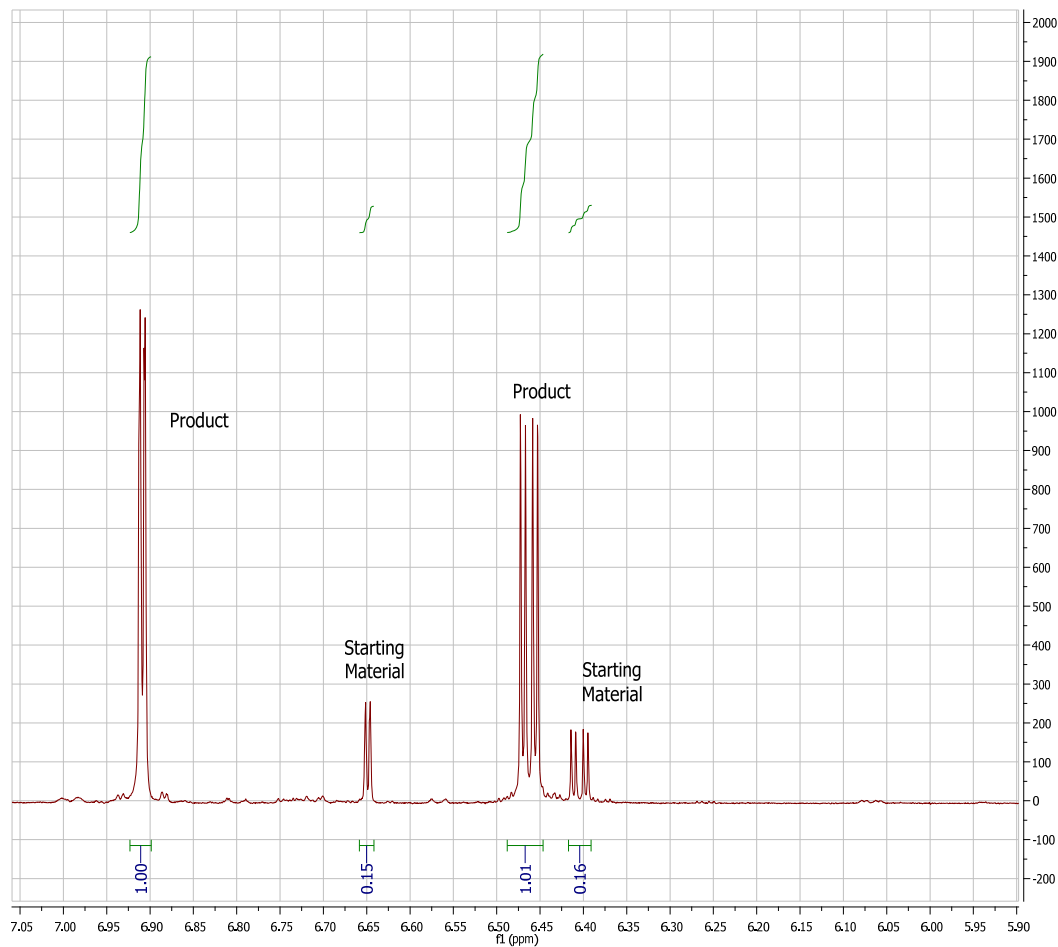
Figure 2.17. GC-FID Calibration Curve for 2-bromopyridine.



**Figure 2.18. GC-FID Calibration Curve for 2-phenylpyridine.**

#### 2.2.3.2 NMR

$^1\text{H}$  and  $^{13}\text{C}$ -NMR



**Figure 2.19. Example  $^1\text{H}$  NMR spectra: reaction of 4-amino-2-bromopyridine with phenylboronic acid under 2 atm.  $\text{CO}_2$  with 40% water, 24 h, after workup.**

NMR spectra were used to determine amount of starting material and product in reaction mixtures after workup by comparison to standards of each compound. NMR Yields were calculated according to the following:

$$\text{NMR Yield} = \frac{I_{\text{Prod.}}}{I_{\text{SM}} + I_{\text{Prod.}}}$$

#### Equation 2.1. NMR Yield Calculation

where  $I_{\text{prod.}}$  and  $I_{\text{SM}}$  denote the area integrals of the product and substrate respectively.

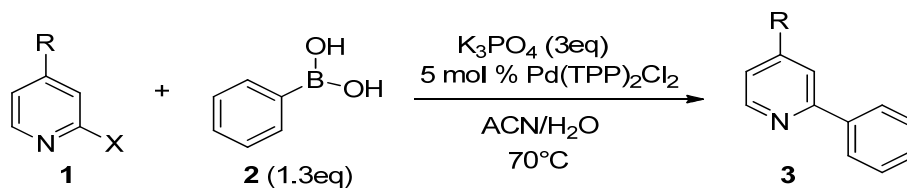
### <sup>31</sup>P-NMR

<sup>31</sup>P-NMR experiments were performed on a Bruker AMX-400 NMR machine using 256 scans. Samples were prepared by adding 0.2mL of sample to 0.3mL of deuterated ACN in a NMR tube. A capillary tube containing an 85% solution of phosphoric acid was used as a reference peak and set to ppm = 0.

## 2.3 Results and Discussion

### 2.3.1 The effect of CO<sub>2</sub> and Volume Percent of Water

As means of demonstrating the effect of CO<sub>2</sub> pressure on Suzuki reaction, reactions were run under varying amounts of CO<sub>2</sub> pressure and under atmospheric N<sub>2</sub> for comparison. Scheme 2.1 shows the reaction scheme for the Suzuki coupling of 4-amino-2-halopyridine and 2-halopyridine with phenylboronic acid using a phosphate base and triphenylphosphine ligand in an acetonitrile (ACN)/water mixture. Reactions under CO<sub>2</sub> pressure are conducted in a 300mL Parr reactor at 70°C. Reactions under N<sub>2</sub> were run in 100mL 3-neck Morton flasks. Detailed protocols and analytical methods are located in the experimental section. The results of the Suzuki coupling of 4-amino-2-halopyridines and 2-halopyridines reactions run in a 25/75 v/v% water and acetonitrile solvent system are shown in Table 2.6.



**Scheme 2.1. Suzuki Coupling Reaction Scheme.**

Both bromo- and chloro- 4-amino-2-halopyridine substrates give poor yield of product under N<sub>2</sub>, yielding only 17% and 21% respectively. In contrast, 2-bromopyridine and 2-chloropyridine give higher yields under N<sub>2</sub> (87% and 100%), respectively. Reactions run under 450psi CO<sub>2</sub> result in 55% and 71% yield of 4-amino-2-

phenylpyridine when 4-amino-2-bromo and 4-amino-2-chloropyridine are used as substrates. These represent substantial increases in yield (30-50% increase) for these substrates compared to yields of reactions run under N<sub>2</sub>. Reactions of 4-amino-2-bromopyridine were also run under 100 and 650psi of CO<sub>2</sub>, giving 50% and 57% yields of product. Neither result is significantly different from the yield of reaction run under 450psi CO<sub>2</sub>.

The Suzuki reaction of 2-chloro- and 2-bromopyridine under N<sub>2</sub> gives yields of 100% and 87% when run under N<sub>2</sub>. Both values are significantly higher than the yields of the aminopyridine analogs run under the same conditions. Interestingly, reactions run under 450 psi of CO<sub>2</sub> result in yields of 29% and 7% for these two substrates, a significant decrease in yield from reactions run under N<sub>2</sub>.

**Table 2.6. Reactions run for 24 hours with 4-amino-2-halopyridines and 2-halopyridines with 25% v/v of H<sub>2</sub>O. (a). Yield calculated from GC-FID calibration curve  
(b). Reaction was run in a 100 mL 3-neck Morton flask**

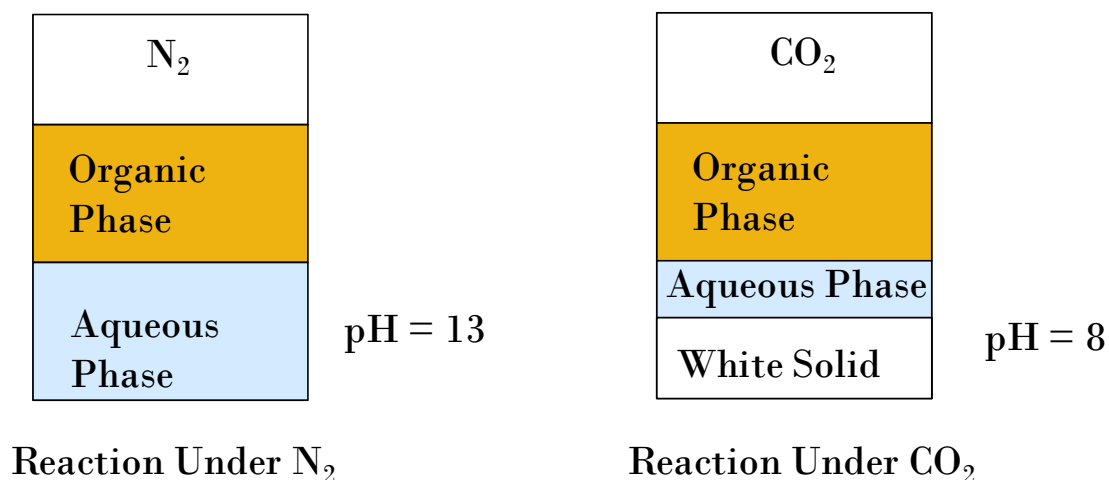
Entry	X=	R=	Atmosphere	Pressure (psi)	Yield (%) <sup>a</sup>
1 <sup>b</sup>	Br	NH <sub>2</sub>	N <sub>2</sub>	Atmospheric	17±4
2	Br	NH <sub>2</sub>	CO <sub>2</sub>	100	50±4
3	Br	NH <sub>2</sub>	CO <sub>2</sub>	450	55±6
4	Br	NH <sub>2</sub>	CO <sub>2</sub>	650	57±2
5 <sup>b</sup>	Cl	NH <sub>2</sub>	N <sub>2</sub>	Atmospheric	21±2
6	Cl	NH <sub>2</sub>	CO <sub>2</sub>	450	71±3
7 <sup>b</sup>	Br	H	N <sub>2</sub>	Atmospheric	87±3
8	Br	H	CO <sub>2</sub>	450	7±0.3
9	Cl	H	N <sub>2</sub>	Atmospheric	100±1
10	Cl	H	CO <sub>2</sub>	450	29

It is important to note that the reaction of 2-bromopyridine under a nitrogen atmosphere was conducted in both a glass round bottom flask and in the Parr reactor

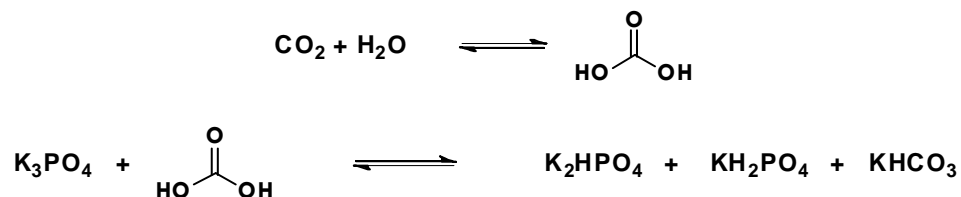


as a means of evaluating the effect of the reaction vessel. These two trials produced negligible differences in product yield. After two hours the yields were 60% and 55% in the glass round bottom and the Parr, respectively. After 18.5 hours the corresponding yields were 80% and 95%. It was concluded that the material making up the reaction vessel made a small difference in yield, but not enough to explain the difference in yield when CO<sub>2</sub> or N<sub>2</sub> is used.

Some observations regarding the reaction systems as a function of the gaseous environment are pertinent at this point (Figure 2.20). (1) Under nitrogen, the reaction systems are composed of two liquid phases: an organic phase and an aqueous phase. In contrast, employing CO<sub>2</sub> in place of nitrogen resulted in the formation of a solid phase in addition to the two liquid phases. Analyses of the solid phase showed that it is composed of potassium carbonate, bicarbonate and phosphate. (2) Reactions under CO<sub>2</sub> resulted in a significant decrease in the volume of the aqueous phase. (3) The pH of the aqueous phase decreased from an initial value of 13 to a value close to 8 with the addition of CO<sub>2</sub>. It is likely that CO<sub>2</sub> reacts with water to form carbonic acid which, in turn, reacts with the base to form carbonate inorganic salts (Figure 2.21). In addition, the presence of solid carbonate and phosphate salts has been shown to cause mass transfer issues, limiting the availability of transfer between organic and aqueous phases and significantly slowing the reaction rate.<sup>29-31</sup>



**Figure 2.20. Phase behavior of the Suzuki coupling system under nitrogen and carbon dioxide.**



**Figure 2.21. Reaction of  $CO_2$  with water and bases to form new inorganic phase composition.**

In order to determine if solid formation was slowing reactivity, reactions were runs with 40 v/v% of water, keeping other reaction parameters constant.

**Table 2.7. Reactions run for 24 hours with 4-amino-2-halopyridines and 2-halopyridines with 40% v/v of H<sub>2</sub>O. (a). Yield calculated from GC-FID calibration curve**  
**(b). Reaction was run in a 100 mL 3-neck Morton flask**

Entry	X=	R=	Atmosphere	Pressure (psi)	Yield (%) <sup>a</sup>
1 <sup>b</sup>	Br	NH <sub>2</sub>	N <sub>2</sub>	Atmospheric	23±4
2	Br	NH <sub>2</sub>	CO <sub>2</sub>	30	83±0
3	Br	NH <sub>2</sub>	CO <sub>2</sub>	100	91±8
4	Br	NH <sub>2</sub>	CO <sub>2</sub>	450	99±2
5 <sup>b</sup>	Cl	NH <sub>2</sub>	N <sub>2</sub>	Atmospheric	30±2
6	Cl	NH <sub>2</sub>	CO <sub>2</sub>	30	93±3
7	Cl	NH <sub>2</sub>	CO <sub>2</sub>	100	98±3
8 <sup>b</sup>	Br	H	N <sub>2</sub>	Atmospheric	92±5
9	Br	H	CO <sub>2</sub>	450	15±0.3
10 <sup>b</sup>	Cl	H	N <sub>2</sub>	Atmospheric	91±1
11	Cl	H	CO <sub>2</sub>	450	32±6

Table 2.7 summarizes the results of Suzuki coupling reactions involving 2-chloro and 2-bromo-4-aminopyridine as well as 2-chloro and 2-bromopyridine in a 60/40(ACN/H<sub>2</sub>O v/v %) solvent system (Scheme 2.1). For both substrates reacted under N<sub>2</sub>, increasing the amount of water had very little effect on the reaction yield. Reactions involving 2-bromo and 2-chloropyridine with 40% H<sub>2</sub>O obtained yields of 92% and 91%, and the 2-bromo and 2-chloroaminopyridine reactions with 40% H<sub>2</sub>O gave yields of 23% and 30%. None of these yields are significantly higher than those in Table 2.6. Physically, the system remained the same as observed with 25% water.

Reactions of 2-bromo- and 2-chloropyridine run under 450psi CO<sub>2</sub> resulted in yields of 15% and 32%. This constitutes a 60-75% decrease in yield compared to reactions run under N<sub>2</sub>. Thus, as was observed for reactions run with 25% water, the application of CO<sub>2</sub> is detrimental to the reactivity of these two substrates. However, the

increase in water does give slightly higher yields compared to reactions run with 25% H<sub>2</sub>O under CO<sub>2</sub> pressure (Table 2.6).

The greatest effect of the increase in water amount is seen with the aminopyridine substrates. The reaction of 2-bromo-4-aminopyridine gives a yield of 99% when run under 450psi of CO<sub>2</sub> pressure. This is a significant increase in yield compared to the 25% water case (55% yield). As with reactions run with 25% water, varying the CO<sub>2</sub> pressure does not have a drastic effect on the reaction yield, for reactions run at 30 and 100 psi give yields of 83% and 91%. Suzuki reactions of 2-chloro-4-aminopyridine under CO<sub>2</sub> also give increased yields when reacted with additional water, obtaining quantitative yields at pressures as low as 30psi of CO<sub>2</sub> (71% with 25% H<sub>2</sub>O and 450psi CO<sub>2</sub>). The ability to maintain reactivity is important from an industrial point of view, for lower operating pressures lower the cost of reactor design.

An important observation is that no significant decrease was observed in the volume of the aqueous layer. Also, no significant formation of solid was observed. This information, combined with the increased yields seen under CO<sub>2</sub> pressure indicate that the additional water was necessary to prevent formation of the solid and promote the reaction under CO<sub>2</sub> pressure.

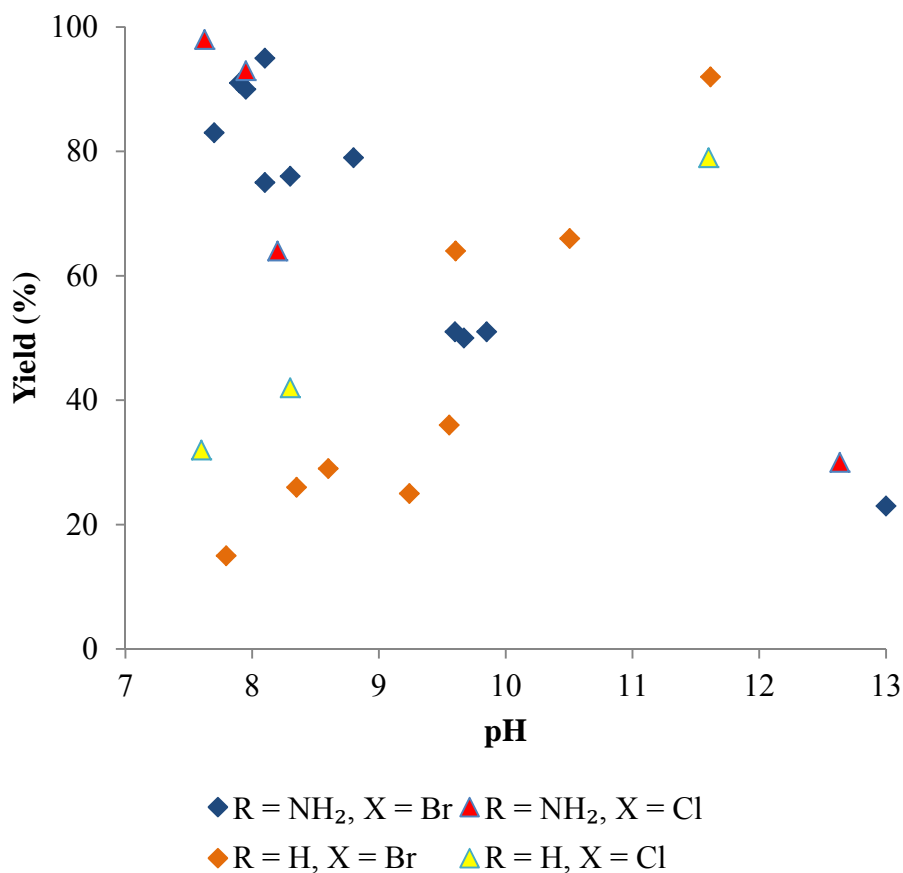
Calibration curves were utilized to determine the yields of reactions in Table 2.6 and Table 2.7. As a means of verifying the accuracy of this analysis, a control experiment was run in which 4-amino-2-bromopyridine was coupled with phenylboronic acid under 450psi of CO<sub>2</sub> pressure and 40% water. GC-FID analysis observed 99% of the coupled product. Isolation by column chromatography yielded 94% of the coupled product

(details in Experimental section) providing confirmation of the accuracy of analysis by GC/calibration curve.

Overall, increasing the amount of water has little effect on reactivity for reactions under  $N_2$ ; however, it greatly improves reaction yields for the two amino-containing substrates reacted under  $CO_2$ , leading to quantitative yields at relatively modest  $CO_2$  pressures. Interestingly, even with an increased amount of water present, the 2-halopyridine compounds obtain lower yields when reacted under  $CO_2$  pressure compared to reactions run under  $N_2$ . These substrates do, however, achieve quantitative yields when reacted under  $N_2$ . The observed solid formation combined with the pH change of the aqueous phase upon the application of  $CO_2$  indicates that increased reactivity of the aminopyridines could be a result of a change in pH due to  $CO_2$  pressure.

### 2.3.2 Effect of pH on Reaction

While the results in the previous section demonstrate the  $CO_2$  pressure has a significant effect on the reactivity of the substrates examined, the application of  $CO_2$  also changes the pH of the reaction system from  $\sim 13$  under  $N_2$ , to  $\sim 8$  when  $CO_2$  is applied (Figure 2.20). As a means of evaluating the effect of pH on the reaction of these substrates, a series of Suzuki reactions were performed using different base systems under  $N_2$  for 24 hours. The yields of these reactions (as well as those run under  $CO_2$  pressure) are plotted as a function of pH in Figure 2.22. More detail on each reaction can be found in experimental.



**Figure 2.22. Yield as a function of pH for 4-amino-2-halopyridines and 2-halopyridines. Follows procedure in Scheme 2.1 except different bases are used in certain cases.**

Figure 2.22 shows a distinct trend for both amino and non-amino-containing substrates over a pH range of roughly 8-13. Both 2-chloro and 2-bromopyridine show lower yields (20%-30%) around a pH of 8. As the pH is increased, the yield of the reaction increases until roughly quantitative yields are reached around a pH of 12. The 2-bromo and 2-chloroamino pyridine substrates show an opposite effect. At a pH around 13, both amino substrates give relatively low yields (20-30%). As the pH is decreased, the yields increase until quantitative yields are reaching around a pH of 8. It is important to note a key difference between the bromo- and chloroaminopyridine substrates. While

the bromo compound has several reactions under N<sub>2</sub> which reach quantitative yields on this graph, the chloro compound's quantitative yields come from reactions run under CO<sub>2</sub> pressure. More data points are needed for the 2-chloro-4-aminopyridine case to clarify the effect pH has on the reactivity of this system. However, based upon the data available, it appears that there is an optimum pH that is substrate specific for these Suzuki coupling reactions. Additionally, it appears that the primary effect of CO<sub>2</sub> on the reactivity is adjusting the pH of reaction.

### 2.3.3 Reaction Progress as a Function of Time

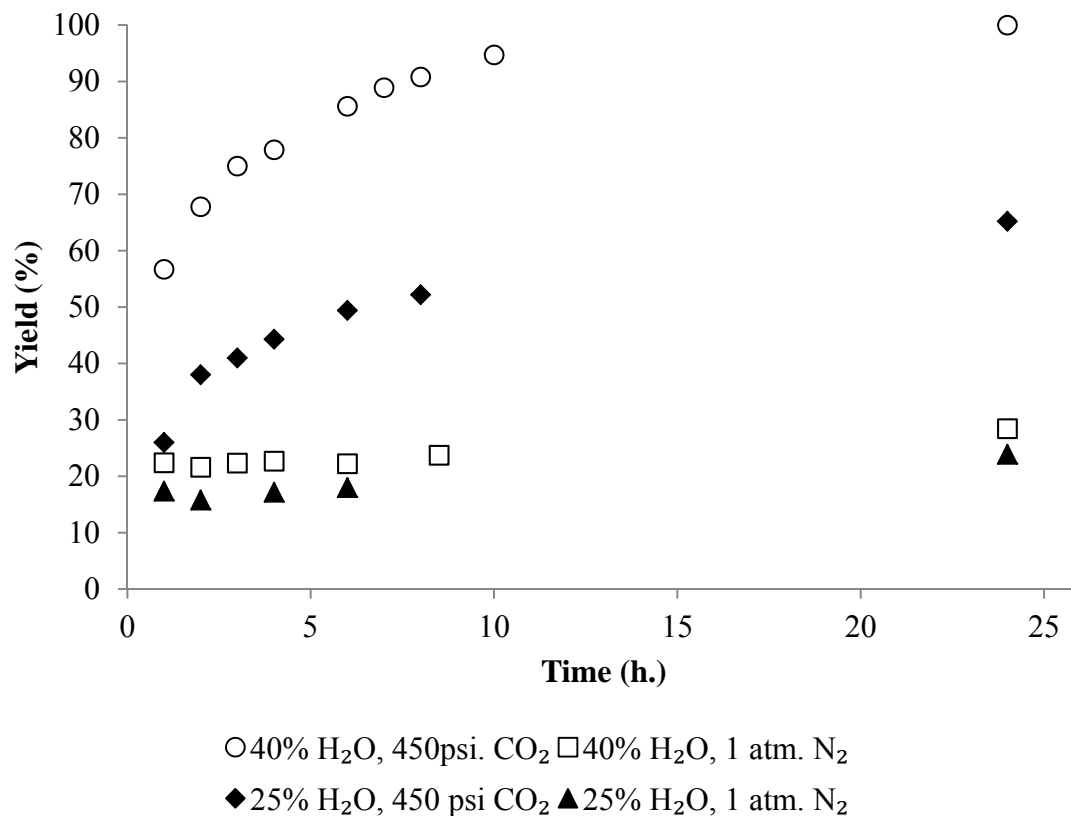
In the preceding sections, the resulting yields after 24 hours of reaction were reported. In order to gain a better understanding of how different reaction conditions would affect the rate of reaction, the formation of products were followed as a function of time.

Figure 2.23 shows the yield of product yield as a function of time for the reaction of 4-amino-2-bromopyridine using both 25/75 and 40/60 v/v% water/ACN solvent systems, and under both atmospheric N<sub>2</sub> and 450psi CO<sub>2</sub>. In every case, the reactions proceed quickly initially, reaching ~20% yield (60% with 40% H<sub>2</sub>O and CO<sub>2</sub> pressure) within the first hour of reaction. However, for the reactions under N<sub>2</sub>, minimal increases in product yield are seen after the first hour. In fact, there is little difference between the results for 25% and 40% water systems under nitrogen. Both reach 15-25% yields within an hour and only reach yields of 20-30% after 24 hours. Considering no solids form in either of these cases, this supports the idea that the presence of solids can slow Suzuki reaction. The reaction under 25% water and 450 psi CO<sub>2</sub> reaches a similar yield after the first hour (26%) as the nitrogen reactions, but reaction continues thereafter producing 65% of the coupled product after 24 hours.

The effect of added water has the largest effect on reactions run under CO<sub>2</sub> pressure. The reaction with 40% water and 450psi CO<sub>2</sub> reaches a much higher yield (60%) after 1 hour than when only 25% water is used (26%). This reaction then proceeds to give 100% yield of product after 24 hours.

Thus, two primary effects are seen 1). The presence of CO<sub>2</sub> allows reaction to continue following the first hour of reaction and 2). When CO<sub>2</sub> is present, the increased amount of water leads to significantly higher reactivity initially, thus allowing for more product formation over 24 hours. This agrees with the idea that the reduced amount of solid leads to higher reactivity, for a significant amount of solids are formed when CO<sub>2</sub> and 25% of H<sub>2</sub>O are present.



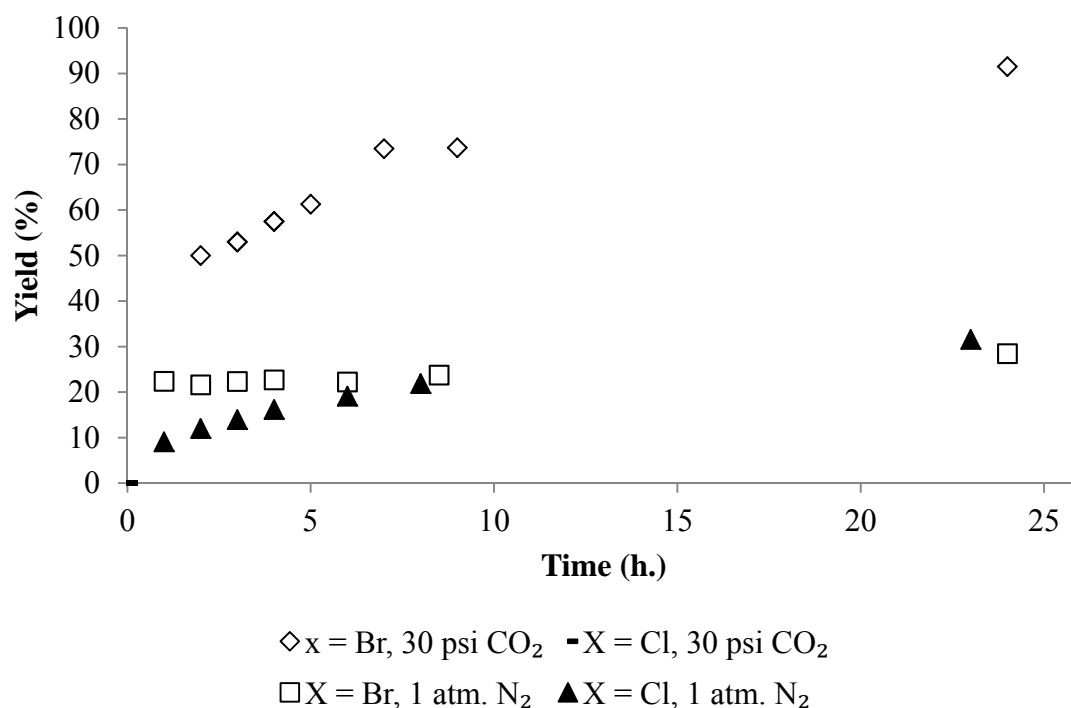


**Figure 2.23. 4-Amino-2-bromopyridine reaction progress as a function of time. % H<sub>2</sub>O is measured as %v/v. Time = 0 corresponds to the reaction system reaching temperature (Scheme 2.1).**

Figure 2.24 shows a comparison of the reactions of 4-amino-2-chloropyridine and 4-amino-2-bromopyridine with 40% H<sub>2</sub>O under both N<sub>2</sub> and 30 psi CO<sub>2</sub>. Under N<sub>2</sub>, the chloro- substrate approaches a ~20% yield asymptotically over 24 hours. In contrast the bromo- substrate reaches 20% within the first hour, but then slows significantly, showing very little improvement in yield at 24 hours.

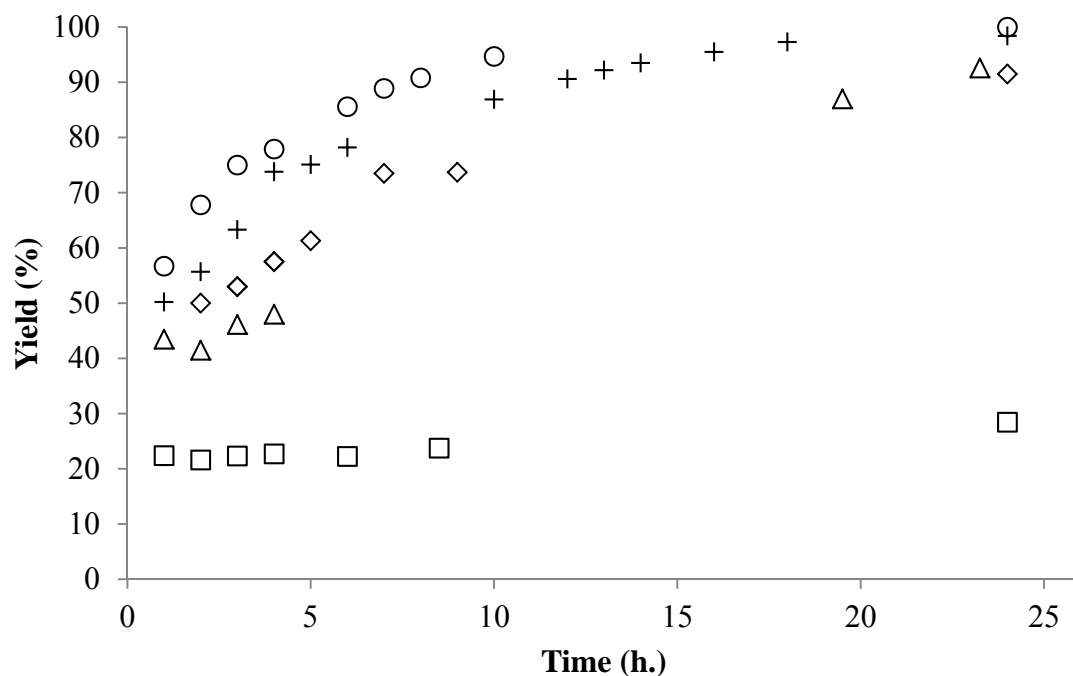
Under 30 psi of CO<sub>2</sub>, both chloro- and bromo- substrates display higher reactivity compared to their reactions under N<sub>2</sub>. After 24 hours, both substrates yield quantitative amounts of coupled product. Interestingly, these two substrates demonstrate essentially

the same product yield vs time profile. This indicates that, under these reaction conditions, the system is halogen independent.



**Figure 2.24. Reaction progress as a function of time for 4-amino-2-halopyridines. Reactions run with 40% v/v water. Time = 0 corresponds to the reaction system reaching temperature (Scheme 2.1).**

Figure 2.25 shows the formation of product vs. time for the Suzuki reaction of 4-amino-2-bromopyridine as a function of CO<sub>2</sub> pressure and base type.

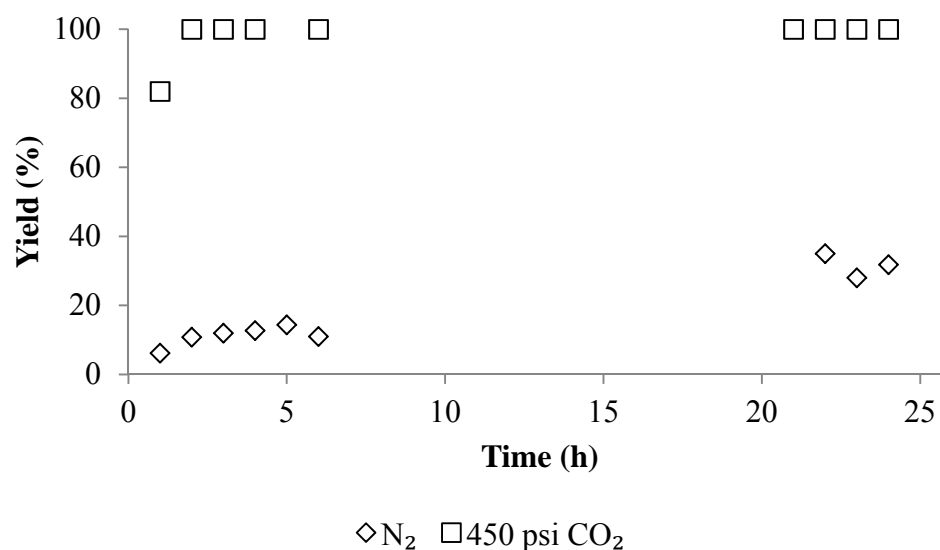


◇ 30 psi CO<sub>2</sub>   ○ 450 psi CO<sub>2</sub>   + 100 psi CO<sub>2</sub>   □ 1 atm. N<sub>2</sub>   △ N<sub>2</sub>, K<sub>2</sub>HPO<sub>4</sub>

**Figure 2.25. Suzuki coupling reaction of 4-amino-2-bromopyridine. Follows Scheme 2.1 except for where K<sub>2</sub>HPO<sub>4</sub> is used as base.**

Reactions run under N<sub>2</sub> (with K<sub>2</sub>HPO<sub>4</sub> as base), 30 psi CO<sub>2</sub>, 100 psi CO<sub>2</sub>, and 450 psi CO<sub>2</sub> (all have a reaction pH of ~8) all show higher product yields after 1 hour compared to the reaction run under N<sub>2</sub> with K<sub>3</sub>PO<sub>4</sub> as base (pH ~12). Additionally, these reactions with a pH of ~8, all continue to show reactivity past 1 hour (not the case for the higher pH reaction). As the pressure of CO<sub>2</sub> increases from 30 to 450psi of CO<sub>2</sub>, there is an increase reaction rate (under 450psi CO<sub>2</sub>: at 8 hours there is a 91%, under 30 psi CO<sub>2</sub>: at 9 hours there is a 74% yield), thus there is some benefit to running reactions under higher pressures of CO<sub>2</sub>; however, all of the reactions reach >90% after 24 hours.

The effect of CO<sub>2</sub> pressure on the rates of reaction for 2-chloropyridine is shown in Figure 2.26. The reactions under N<sub>2</sub> display a much higher initial rate, yielding 81% of the coupled product after 1 hour. In fact, the reaction reached completion in 2 hours. However, under 450 psi CO<sub>2</sub> the rate is significantly decreased; only 6% product is observed after 1 hour, and product amount only increases marginally to 32% after 24 hours. Thus, this data further demonstrates the detrimental effects of CO<sub>2</sub> pressure on this reaction.

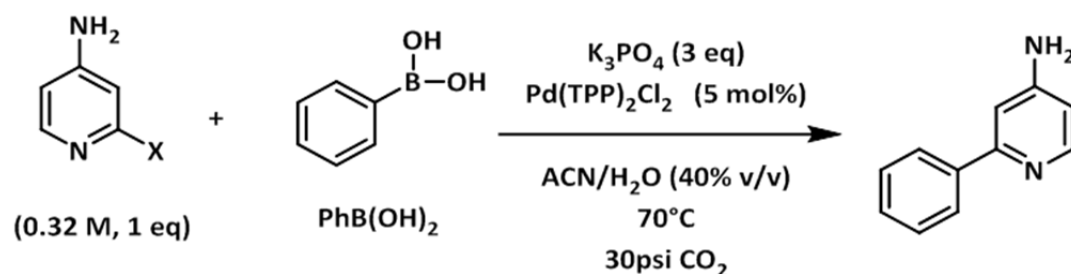


**Figure 2.26. Reaction progress as a function of time for 2-chloropyridines. Follows Scheme 2.1. Reactions run with 40% v/v water. Time = 0 corresponds to the reaction system reaching temperature.**

#### 2.3.4 Effect of Phenylboronic Acid Concentration

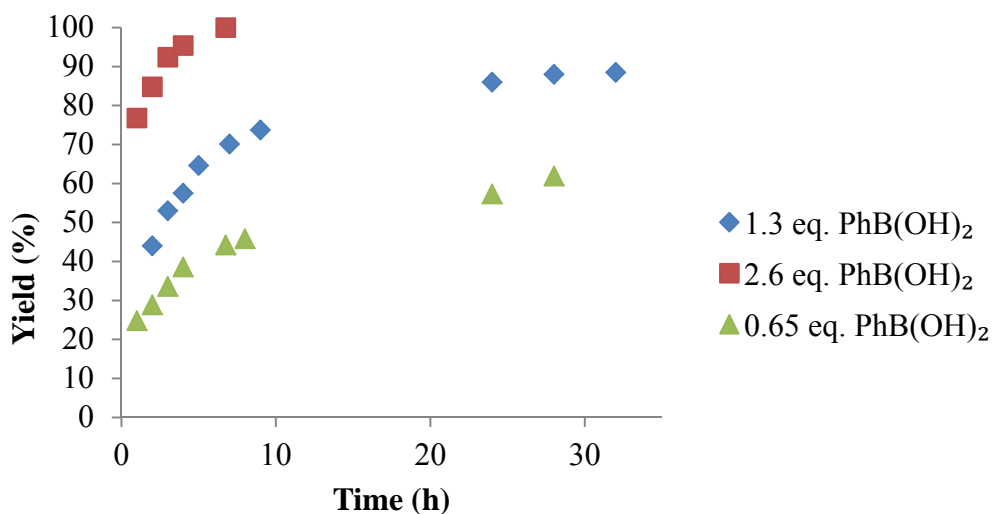
While many believe that the boronic acid species must be “activated” via an attack from an anion, creating a “boronate” compound,<sup>32</sup> evidence does exist suggesting

that this attack is may not be necessary and the non-activated boronic acid serves as the active species (Figure 2.3).<sup>13</sup> This distinction is important as it pertains to this work, for pH plays a crucial role in the amount boronate species present at equilibrium. The boron nucleophile is only involved in the transmetalation step of the catalytic cycle, so if transmetalation were the rate determining step, the pH effect on yield could simply be due to changes in the equilibrium of the boron species. Thus, experiments were carried out in which the amount of phenylboronic acid was varied in order to determine its role in the reaction mechanism. The complicated nature of this reaction system (multiphase reaction system, multiple catalytic steps, difficulty of tracking intermediates of the catalytic cycle, behavior of molecules at different pHs, catalyst degradation) make quantifying a catalytic rate expression and determining reaction mechanisms a difficult task. However, some insights into how substrate amount affects reactivity can be gained.



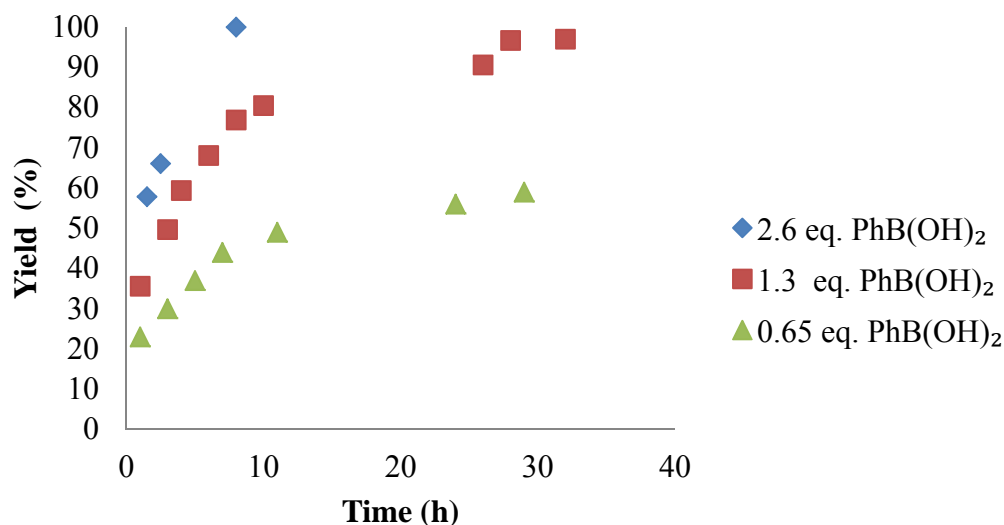
**Scheme 2.2. Reaction varying initial phenylboronic acid concentrations.**

Reactions were run under CO<sub>2</sub> pressure with substrates 4-amino-2-bromo- and 4-amino-2-chloropyridine where the amount of phenylboronic acid initially present was varied (Scheme 2.2).



**Figure 2.27. Phenylboronic acid effect on 4-amino-2-bromopyridine reactions under CO<sub>2</sub> pressure. Scheme 2.2. X = Br.**

Figure 2.27 shows these results for the reaction of 4-amino-2-bromopyridine with 0.65, 1.3, and 2.6 eq. of phenylboronic acid. At 4 hours, these reactions give yields of 39%, 58%, and 95%, respectively. Thus, it is shown that adjusting the amount of phenylboronic acid present has a significant increase in reactivity.



**Figure 2.28. Phenylboronic acid effect on 4-amino-2-chloropyridine reactions under CO<sub>2</sub> pressure. Scheme 2.2. X = Cl. Yield based on pyridine Substrate.**

Figure 2.28 shows these results for the reaction of 4-amino-2-chloropyridine with 0.65, 1.3, and 2.6 eq. of phenylboronic acid present. Once again, a correlation is seen between phenylboronic acid amount and reaction yield. At 11 hours, reaction run with 0.65 eq. phenylboronic acid reaches yields of 49%. At 8 hours, reactions run with 1.3 and 2.6 eq. of phenylboronic acid give 77%, and 100% yields, respectively.

There are a number of possible explanations for this behavior. Since phenylboronic acid is involved in the transmetalation step of the Suzuki mechanism, the trends seen in these experiments could be a result of this step being rate-limiting. However, it is believed that boronic acid compounds can play a key role in reducing pre-catalysts to their active form,<sup>33</sup> so it is not unreasonable to think that varying the amount of phenylboronic acid present initially has an impact on the amount of catalyst that is activated. Finally, phenylboronic acid has a pKa of 8.8. The amount of this compound

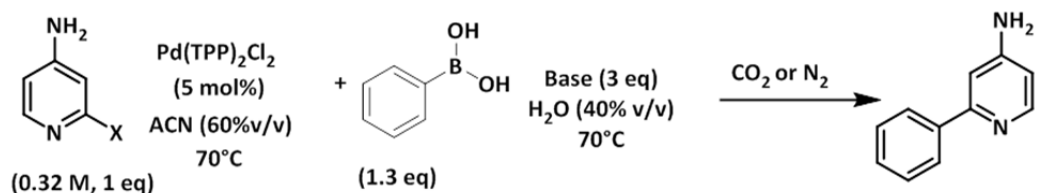
will have an effect on the acid/base behavior of this system and therefore the pH. Unfortunately, the boronic acid and corresponding boronate will partition between the two phases, can undergo homocoupling to form biphenyl, and is known to exist in equilibrium with a trimer configuration.<sup>34</sup> Thus, trying to study its role further proves difficult.

While it may be difficult to interpret the exact mechanistic role of phenylboronic acid in this reaction system, it is clear that increasing the amount of phenylboronic acid present can reduce the time needed to reach quantitative yield significantly (from 24 to 7 hours in some cases). From an industrial point of view, this is important, for phenylboronic is significantly cheaper than both the aminopyridine substrate and palladium, and the reaction produces a very expensive product (4-amino-2-phenylpyridine). Thus, an additional, inexpensive means of improving reactivity was determined.

#### 2.3.5 Early Reaction Behavior/Catalyst Tracking

Previous sections have established that a substrate-specific reaction pH exists in the Suzuki coupling reactions studied. It is particularly interesting that the more basic aminopyridines show higher reactivity at pHs of ~8. While experiments shown previously which track the reaction progress as a function of time gives some insight, a significant amount of reactivity occurs before the first sample is taken (1 hour). As a means of gathering kinetic data at earlier time periods, a modified procedure was used to conduct Suzuki reactions and track product development over time.

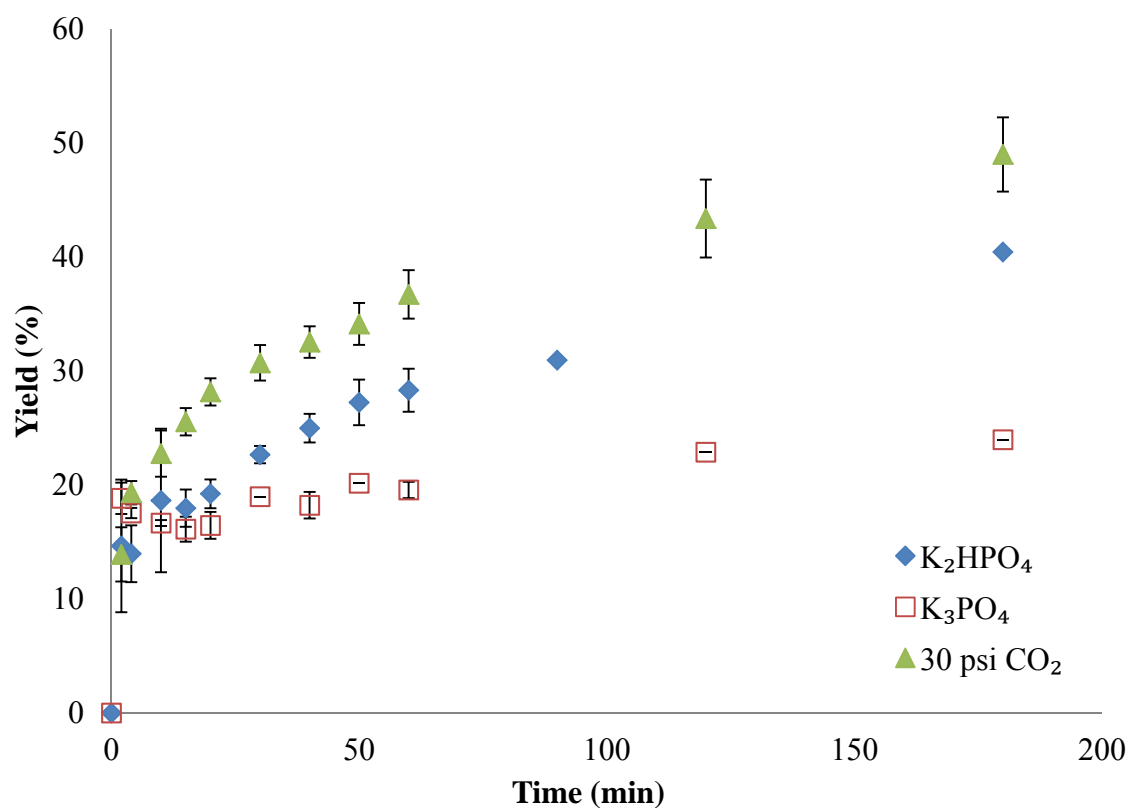




**Scheme 2.3. Modified Reaction Scheme.**

The new protocol follows Scheme 2.3. The addition of reactants at reaction temperature ( $70^\circ\text{C}$ ) ensures that no reaction has occurred before time 0. In contrast to previous reaction vs. time studies, samples were taken at earlier time periods ( $t < 1$  hour) and analyzed by GC-FID for reaction yield and  $^{31}\text{P}$ -NMR to characterize catalyst state. The general procedure was as follows: Two solutions : one containing catalyst, substrate, and acetonitrile, and a second solution containing phenylboronic acid, base, and water - were heated to  $70^\circ\text{C}$  and then combined. In a typical reaction, the palladium catalyst (0.08 mmol) was placed in a 3-neck, 100 mL Morton flask (Flask A). Solid substrates (16 mmol) were combined with the catalyst in Flask A. In a separate flask (Flask B), were loaded phenylboronic acid (20.8 mmol) and potassium phosphate (48 mmol). The flasks were then evacuated and backfilled with Argon. Degassed acetonitrile (30 mL) was then added to Flask A and degassed water (20 mL) was added to Flask B. The flasks were then heated to  $70^\circ\text{C}$  with stirring. The contents of Flask B were then transferred to Flask A at temperature via an air tight syringe. This point was denoted as time = 0. Samples (0.2 mL) were taken from the organic phase at periodic intervals and diluted with methanol (0.8 mL) for GC-FID analysis. Additionally, samples were diluted with deuterated ACN and analyzed via P-NMR.

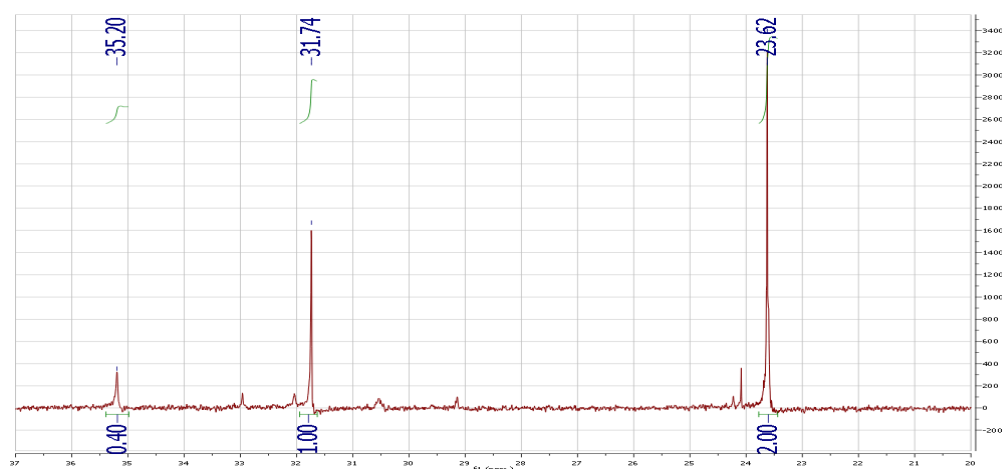
Reactions under CO<sub>2</sub> followed a similar procedure except that the substrate, catalyst, and ACN were heated under CO<sub>2</sub> in a Parr reactor, while the base, boronic acid, and water were heated under nitrogen and then added to the Parr through a chamber pressurized with CO<sub>2</sub>. This denoted time = 0. Sampling of these reactions followed the same procedure as previous yield vs. time reaction studies.



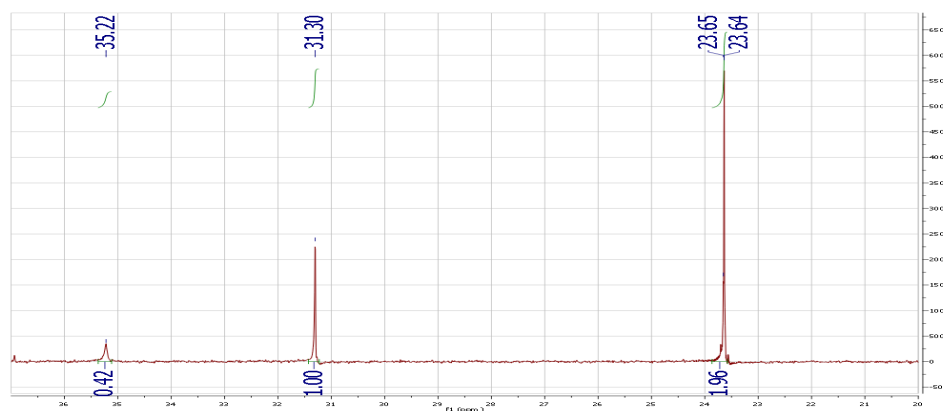
**Figure 2.29. Early kinetic data. Follows Scheme 2.3. X = Br.**

The results for the reaction of 4-amino-2-bromopridine under N<sub>2</sub> with K<sub>2</sub>HPO<sub>4</sub> base, N<sub>2</sub> with K<sub>3</sub>PO<sub>4</sub> base, and under 30 psi CO<sub>2</sub> pressure with K<sub>3</sub>PO<sub>4</sub> are shown in

Figure 2.29. Initially, all reaction conditions give similar yields (15-20% in the first 10 minutes); however as the reaction proceeds the  $K_3PO_4$  reaction (pH of 13) slows considerably compared to those run under  $CO_2$  or with dibasic potassium phosphate (pH of 8) who proceed at very similar rates. This graph indicates that all reaction conditions exhibit activity initially, but at a higher pH (pH = 12), the lack of subsequent product formation indicates catalyst deactivation following the first few minutes of reaction.



**Figure 2.30.  $^{31}P$ -NMR of sample taken from  $K_2HPO_4$  (pH: 8) reaction at 1 hour.**



**Figure 2.31.**  $^{31}\text{P}$ -NMR of sample taken from  $\text{K}_3\text{PO}_4$  (pH: 13) reaction at 1 hour.

$^{31}\text{P}$ -NMR was used as a means to attempt to detect catalyst deactivation. Figure 2.30 and Figure 2.31 show  $^{31}\text{P}$ -NMR results following 1 hour reaction time at a reaction pH of 8 and 13. NMRs were run in acetonitrile using 85% phosphoric acid as a reference peak. While the reaction rates are different at 1 hour, both NMRs show TPP-oxide peaks (35 and 31ppm), a Pd-bound phosphine peak (23.6ppm), and a free TPP peak (-6ppm, not shown). Attempts were made to quantify the relative heights of each peak using an internal standard; however, relaxation times of the substances in solution were too long to accurately quantify the peak intensities. Thus, the  $^{31}\text{P}$ -NMR results are inconclusive, but do not rule out catalyst deactivation at higher pH.

## 2.4 Conclusions

The work in this chapter demonstrates that the application of  $\text{CO}_2$  pressure combined with adjusting the quantity of water in the reaction system leads to quantitative yields for the 2-bromo- and 2-chloro-4-aminopyridines. The protocol described requires only mild reaction conditions (30psi  $\text{CO}_2$  pressure, 70 C), inexpensive and readily

available triphenylphosphine ligand, and relatively inexpensive solvents (ACN and H<sub>2</sub>O). In addition, when reacted under CO<sub>2</sub> pressure, the less expensive 4-amino-2-chloropyridine proceeds at a comparable rate as its bromo counterpart. These same two substrates achieve poor (~20%) yields when reacted under a N<sub>2</sub> atmosphere. It is also seen that increasing CO<sub>2</sub> pressure leads to an increase in reaction rate, thus causing reaction to achieve quantitative yield more quickly.

Interestingly, the less basic, 2-bromo- and 2-chloropyridine substrates achieve quantitative yields when reacted under N<sub>2</sub>, but poor yields (10-30%) when reacted under CO<sub>2</sub> pressure.

Further investigation reveals that the different performance of these reactants under different gaseous environments is due to a difference in reaction system pH under these different environments. The addition of CO<sub>2</sub> triggers acid-base reactions in the aqueous phase, effectively buffering the reaction system at a pH of about 8. Reactions run under N<sub>2</sub> show a pH of 8 to be optimum for the Suzuki reaction of 2-halo-4-aminopyridines. In contrast, the 2-halopyridines react poorly at this same pH, but achieve high yields at higher pH regime (12-13). Thus, the existence of a substrate-specific pH in Suzuki coupling reactions is revealed.

Investigation into reaction progress over time reveals a few key items. When reacted under CO<sub>2</sub> pressure, the less expensive 4-amino-2-chloropyridine proceeds at a comparable rate as its bromo counterpart, increasing CO<sub>2</sub> pressure appears to increase the reaction rate of 4-amino-2-bromopyridine, and increasing phenylboronic acid amount also increases the reaction rate of this compound. All of these results are important when considering optimum process design for the reaction of these types of substrates.

Studying the effect of different reaction conditions ( $\text{CO}_2$  pressure, pH) on the reactivity of 4-amino-2-bromopyridine at earlier time periods ( $<1\text{hr}$ ) shows that, regardless of pH, the reaction achieves  $\sim 20\%$  yield within the first 5 minutes of reaction; however, reactions with a pH of  $\sim 8$  continue to show reactivity. When the reaction has a pH of  $\sim 12\text{-}13$ , reactivity essentially stops. Based on this behavior, it is conjectured that a pH of 8 benefits this reaction system through protonation of the basic reaction product (4-amino-2-phenylpyridine,  $\text{pK}_a = 8.2$ ). This would reduce the amount of product coordinated with the Pd catalyst, thus allowing the catalyst to continue to enter the catalytic cycle as product is formed. This theory also agrees with the observation that reactions with a higher pH (12-13) show reactivity initially, but then slow considerably, for the unprotonated product in the system ligates with and effectively poisons the Pd.

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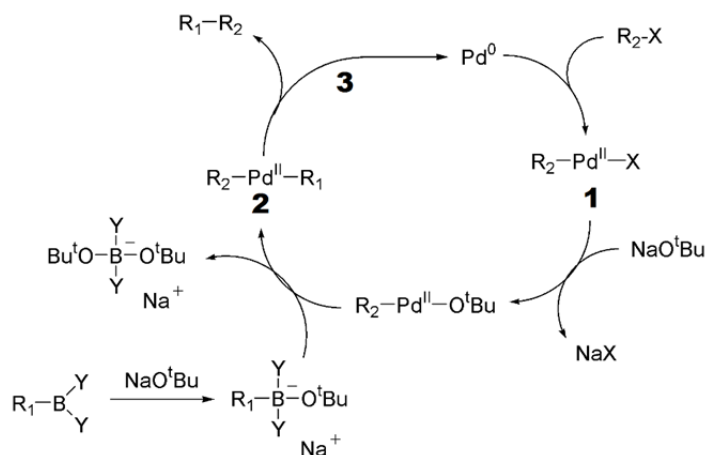


## **CHAPTER 3 - RECOVERY OF PALLADIUM FROM SUZUKI COUPLING MIXTURES USING ORGANIC/AQUEOUS TUNABLE SOLVENTS (OATS) AND SULFUR-CONTAINING ADDITIVES**

### **3.1 Introduction**

#### **3.1.1 Suzuki Coupling Reaction**

The Suzuki-Miyaura coupling reaction (Figure 3.1), a Pd-catalyzed coupling of an organoboronic acid/ester with an organic halide, is a highly-desirable synthetic method for forming C-C bonds. This reaction is desirable, for successful reaction can be achieved using relatively safe, easily accessible reagents and facile reaction conditions. Additionally, the Suzuki reaction tolerates the presence of a wide range of functional groups on reaction substrates.<sup>1-4</sup> For these reasons, the Suzuki coupling reaction has found widespread use in the pharmaceutical and agrosience industries as a key step in the synthesis of many high-value products.<sup>5-7</sup>



**Figure 3.1. Suzuki coupling reaction mechanism.**<sup>8-9</sup>

### 3.1.2 Separation of Pd from Suzuki Reaction Product.

The separation of Pd catalyst from reaction product is a key step in processes involving the Suzuki coupling reaction. For industrial applications, the presence of Pd-catalyst and the end-use of the reaction products necessitate separation of the catalyst from reaction product following the reaction. Federal regulations limit the amount of platinum group metals (PGMs), including palladium, present in pharmaceutical products<sup>10</sup>. For instance, the European Agency for the Evaluation of Medicinal Products limits the amount of palladium in pharmaceutical compounds to <10ppm.<sup>11</sup> Furthermore, palladium is an expensive metal, with prices fluctuating between \$20,000 and \$30,000 per kg in 2014.<sup>12</sup> If recovered, palladium catalysts can be submitted to specialized recycling centers for credit towards reduced cost of new catalyst. Thus, there is significant motivation to separate Pd from reaction product following reaction.

Given these constraints, intelligent process design calls for the implementation of catalysts that are both highly reactive and recoverable. Homogenous catalysis offers increased reaction rates (compared to heterogeneous catalysis); however, catalyst separation is often much more difficult<sup>13</sup>. A further challenge is presented by the heterocyclic, biaryl nature of many pharmaceutical and agrosience products formed by Suzuki reactions.<sup>6,14-17</sup> These types of compounds are known to coordinate with palladium making separation more difficult.

One method of overcoming the difficulty of separating homogenous catalysts is the use of water-soluble ligands. These ligands result in a water-soluble catalyst that maintains high activity and favorable separation from organic reaction products. A limitation exists with strategy in that these ligands are often expensive or difficult to synthesize.<sup>18-19</sup>

The use of coordinating, non-reactive compounds as additives has also seen a great deal of success in the literature for the removal of palladium from heteroaromatic products; however, these types of separations often necessitate the use of expensive solvents.<sup>10,20</sup> Use of coordinating, non-reactive additives in OATS processes could prove equally useful, perhaps even more efficient due to the tunable nature and OATS and inexpensive solvents used.<sup>21-22</sup>

### 3.1.3 OATS Technology

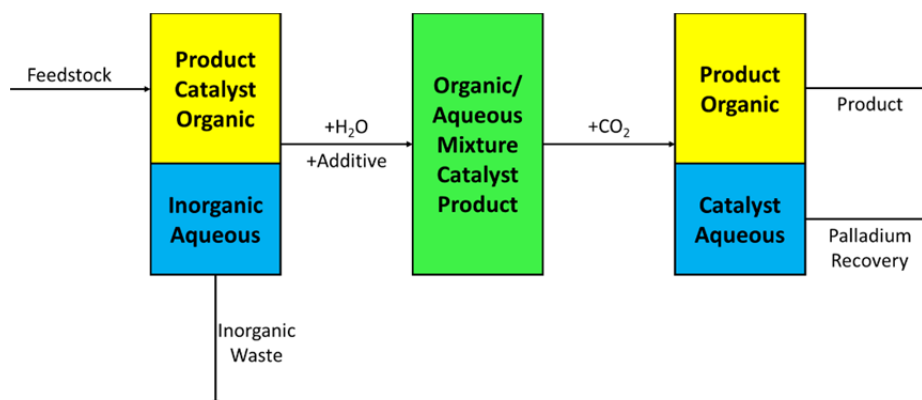
Organic/Aqueous Tunable Solvents (OATS) represent a class of solvents that offer potential solutions to the challenges described above.<sup>23-24</sup> OATS are ternary solvent systems comprised of water, a water-miscible organic solvent and an anti-solvent gas (e.g. water/THF/CO<sub>2</sub> or water/acetonitrile/CO<sub>2</sub>). These systems are unique in that, once

CO<sub>2</sub> pressure is applied, the liquid reaches a cloud point, eventually splitting into two liquid phases. The phase split results in an aqueous-rich phase containing negligible amounts of CO<sub>2</sub> and an organic-rich, gas-expanded liquid layer. OATS offers the ability to conduct homogeneous reactions and heterogeneous separations. An example of such a process is shown by Hallet *et al*, wherein hydrophilic catalyst is recovered from the homogeneous hydroformylation reaction of octene in THF/H<sub>2</sub>O using moderate pressures of CO<sub>2</sub>.<sup>25</sup>

#### 3.1.4 Application of OATS to Suzuki Systems

Application of OATS as a tool for removing palladium from Suzuki coupling mixtures requires a few modifications from its traditional implementation. While many Suzuki coupling reactions have been conducted using organic bases, the vast majority implement much cheaper inorganic bases such as potassium carbonate and potassium phosphate. These salts often initiate a phase split between the specified organic solvent and water without the addition of anti-solvent, thus negating many of the benefits of tunable solvent systems. It is therefore necessary to remove these salts before OATS processing in the cases where inorganic base is used.

Figure 3.2 is a process flow diagram utilizing OATS for the removal of palladium from Suzuki coupling products. The process is broken into 3 primary steps: 1.) Suzuki coupling reaction and subsequent decantation of the salt-rich aqueous phase 2.) Treatment of the organic palladium- and product-rich phase with additional solvent and additive (to influence Pd hydrophilicity), which generates a single working phase and 3.) Addition of CO<sub>2</sub>, which forms distinct product-rich and palladium-rich phases, allowing separation.

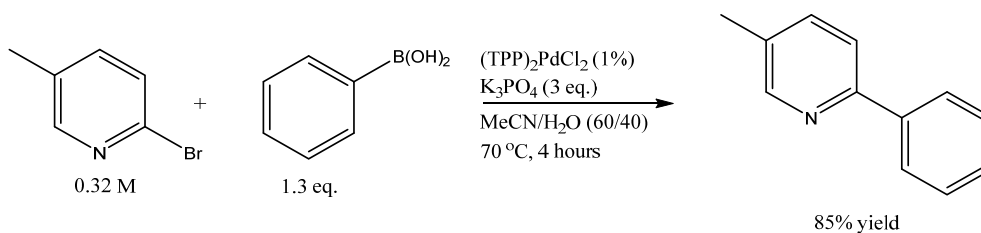


**Figure 3.2. Process Flow Diagram for OATS Implementation in Suzuki Coupling Processes.**

### 3.1.5 Selection of Suzuki Reaction

For separation studies, it was important to find a Suzuki coupling reaction which would produce a basic, heteroaromatic product (making it likely to coordinate with Pd) to simulate the more difficult separations seen in pharmaceutical and agrosience processes. Additionally, an inexpensive ligand and solvent system were desired. Finally, it was vital for the Pd catalyst to remain soluble in the organic phase following reaction, thus, avoiding catalyst losses due to insolubility and removal of inorganic waste (Figure 3.2).

Scheme 3.1 describes the Suzuki coupling of 2-bromo-5-methylpyridine with phenylboronic acid in the presence of bis(triphenylphosphine)palladium chloride and potassium phosphate in acetonitrile and water.



**Scheme 3.1. Suzuki coupling of 5-methyl-2-bromopyridine.**

This reaction is an ideal model with which to investigate the application of OATS towards the recovery of palladium catalysts used in Suzuki couplings, for it fits all of the desired criteria. It reaches 80-90% yields of the basic, heteroaromatic 5-methyl-2-phenylpyridine within 4 hours, using a triphenylphosphine ligand. This ligand is, in general, much cheaper than specialty ligands required in many Suzuki syntheses and is already employed as a preferred ligand at an industrial scale.<sup>26-28</sup> The solvent system is relatively inexpensive, and the ACN/H<sub>2</sub>O system is known to be amenable to OATS technology. Finally, following reaction, the palladium catalyst remains soluble in the organic phase with negligible solubility in the salt-rich aqueous phase following reaction.

### 3.1.6 Selection of Additives

In order to effectively manipulate the hydrophilicity of palladium under application of CO<sub>2</sub>, a variety of additives were screened as possible palladium chelants.

The names and structures of these additives are given in

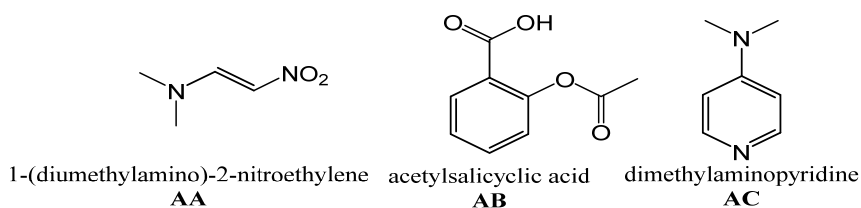
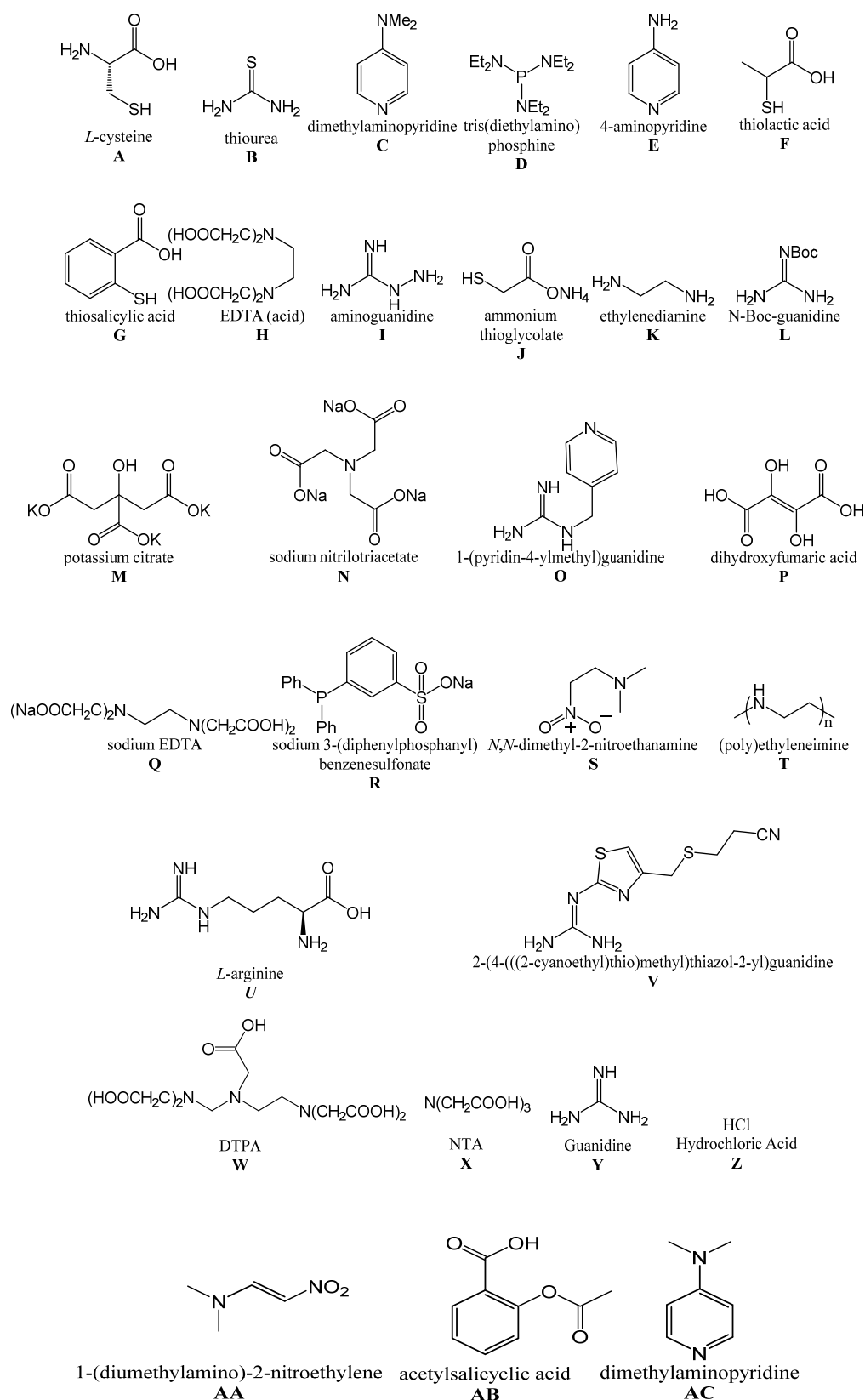


Figure 3.3.



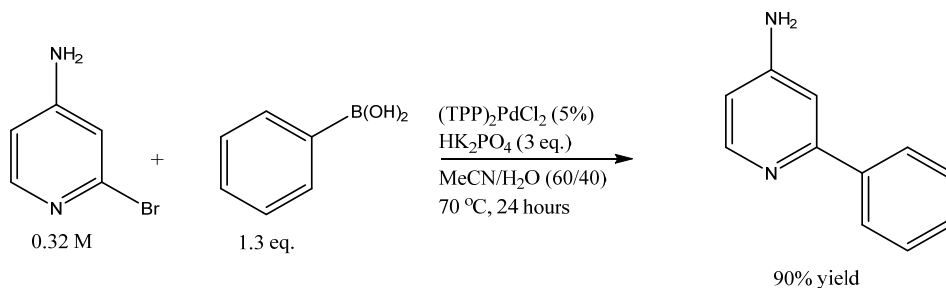
**Figure 3.3. Additives screened for Pd removal**



Among the classes of compounds screened are: amino acids, guanidines, phosphines, polyamines, polyacids, thiols, pyridines and ionic salts. The separation case where no additive is present is also explored in order to determine a baseline of palladium hydrophilicity in this system.

### 3.1.7 Substrate Scope Expansion

A brief investigation into separation of Pd from 4-amino-2-phenylpyridine through OATS technology was also explored. This substrate is more electron-rich than 2-bromo-5-methylpyridine. Thus, it should coordinated more readily with Pd and potentially present a more difficult separation. The reaction scheme for production of this compound is shown in Scheme 3.2.



**Scheme 3.2. Suzuki Coupling Reaction of 4-amino-2-bromopyridine with Phenylboronic Acid.**

An important difference in this reaction is the use of dibasic potassium phosphate instead of the tribasic potassium phosphate used in the coupling of 2-bromo-5-methylpyridine reaction. The weaker base was chosen in response to findings from Senter *et al* concerning the effect of pH on the reactivity of pyridines in Suzuki coupling

reactions.<sup>4</sup> Additionally, 5mol% catalyst and 10mol% TPP are used. The ligand and solvent system remains the same.

## 3.2 Experimental Section

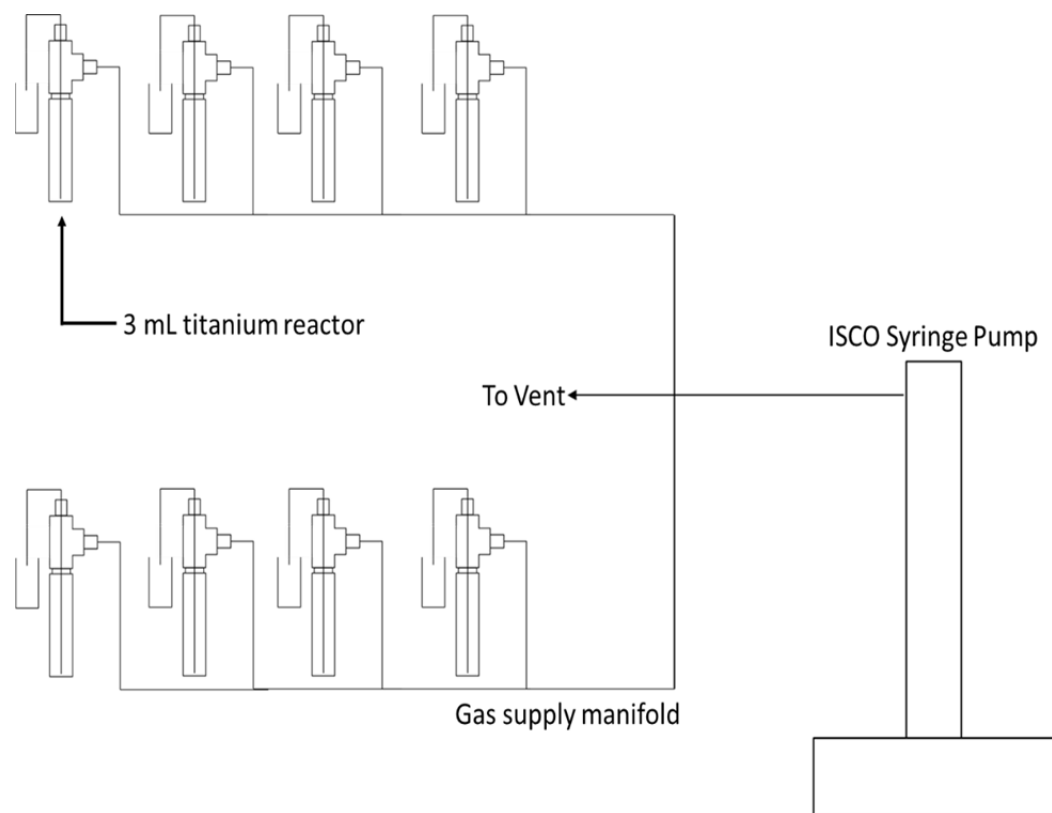
### 3.2.1 Materials

Deionized water was prepared in-house and used throughout the course of the described experiments. Before use, the water was degassed by sparging with N<sub>2</sub> for 30 minutes. Acetonitrile was purchased from Sigma-Aldrich and degassed by N<sub>2</sub> sparge before use. Bis(triphenylphosphine)palladium(II) dichloride, potassium phosphate, and phenylboronic acid were purchased from Sigma-Aldrich and used as received. 2-bromo-5-methylpyridine was purchased from Matrix Scientific and used as received. Throughout the course of this study, many additives were purchased from commercial chemical suppliers and used as received. SFE-grade CO<sub>2</sub> was purchased from Airgas and used as received.

### 3.2.2 Experimental

#### *3.2.2.1 Design of Combinatorial Screening Apparatus*

Large-scale screening of additives was conducted using a combinatorial apparatus built in-house, shown in Figure 3.4.

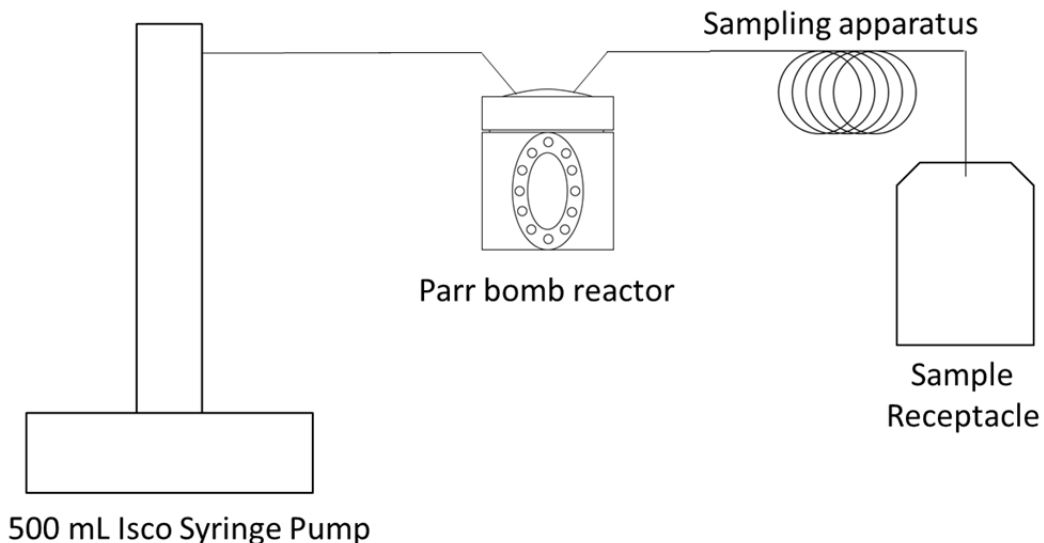


**Figure 3.4. Schematic of Combinatorial Apparatus Built In-House for High-Pressure Sampling of Multiple Mixtures.**

The apparatus consists of eight 3-mL titanium cells, each with an ID of approximately  $\frac{1}{4}$ ". Each cell is fitted with a  $\frac{1}{8}$ " street tee. A  $\frac{1}{16}$ " stainless steel tube was attached to the side of each tee in order to deliver a constant pressure of gas to the headspace. Each  $\frac{1}{16}$ " gas supply tube was attached to a manifold constructed with  $\frac{1}{16}$ " stainless steel tubing and  $\frac{1}{16}$ " crosses purchased from High Pressure Equipment Company. The manifold was also equipped with a valve with which pressure can safely be relieved in the event of an emergency, as well as a transducer with which the system pressure can be monitored. The manifold was supplied with CO<sub>2</sub> via an ISCO Teledyne 260D syringe pump.

### 3.2.2.2 Design of High-Pressure Parr Sampling Apparatus

A 300 mL windowed Parr benchtop reactor was used to screen additives as a function of pressure. The schematic of this system can be seen in Figure 3.5.



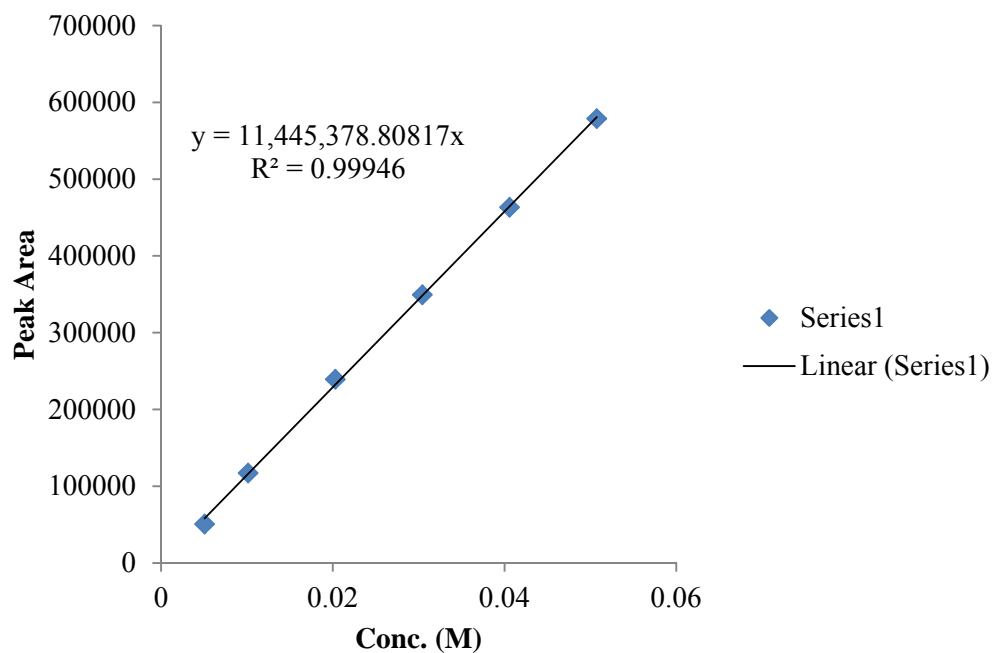
**Figure 3.5. Schematic of Parr Reactor Sampling Apparatus.**

The apparatus consists of the 6-port windowed Parr reactor attached to an upstream Teledyne ISCO 500D syringe pump (for the delivery of CO<sub>2</sub> pressure) and a downstream Valco 6-port stainless steel HPLC sampling valve. This valve was used in conjunction with a sample loop composed of stainless steel tubing at a known internal volume (1.21 mL). Connections were made to the 6-port valve to allow sampling of each liquid phase within the reactor, isolation of a known volume of solution, and subsequent removal and rinsing of collected samples into a sample receptacle.

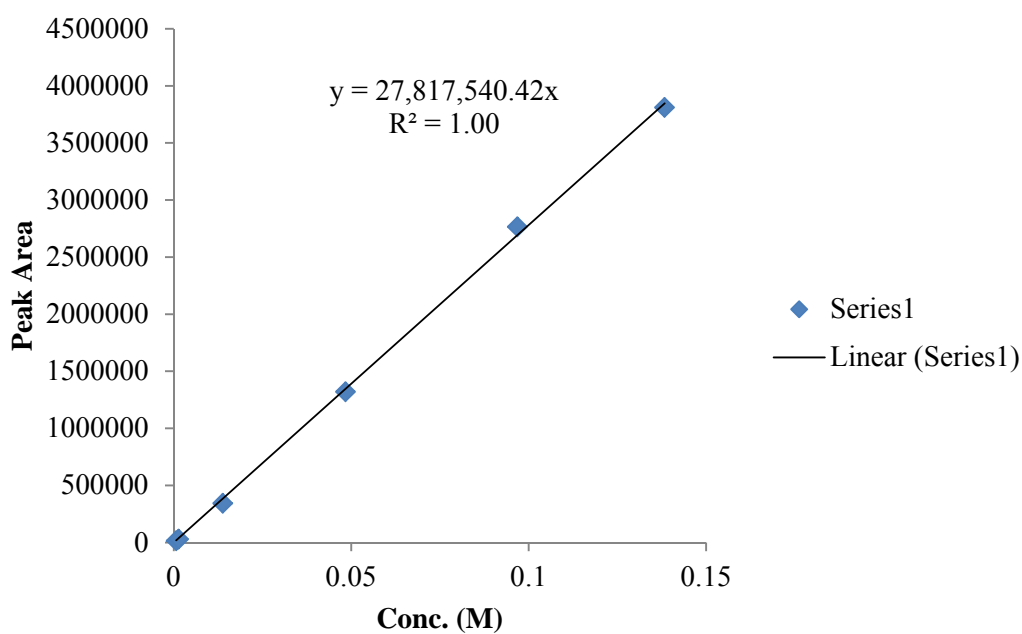
The Parr reactor itself was equipped with two  $\frac{3}{4}$ " quartz glass windows, three sampling ports equipped with 1/16" stainless steel tubing for sampling from various heights in the reactor (aqueous dip tube, organic dip tube, headspace), a Druck pressure transducer calibrated between 0 and 1000 psi, a thermocouple, as well as a burst cap (~2000 psi) to guarantee safety of the Parr operators. A cathetometer was used to measure liquid meniscus heights within the reactor in order to accurately determine volumes.

#### *3.2.2.3 Suzuki Coupling of 2-bromo-5-methylpyridine*

2-bromo-5-methylpyridine (16 mmol, 2.7523 g) was added to a 100 mL 3-neck round-bottomed flask along with phenylboronic acid (1.3 eq., 2.5361 g), tripotassium phosphate (3 eq., 10.1890 g), and bis(triphenylphosphine)palladium(II) dichloride (1 mol%, 112.3 mg). The reaction flask was flushed with N<sub>2</sub> for 15 minutes prior to solvent addition. After flushing with inert gas, 30 mL of degassed acetonitrile and 20 mL of degassed H<sub>2</sub>O were added using air-tight syringes. The mixture was then heated to 70 °C and allowed to react for 5 hours with magnetic stirring (85% yield by GC using calibration curve).



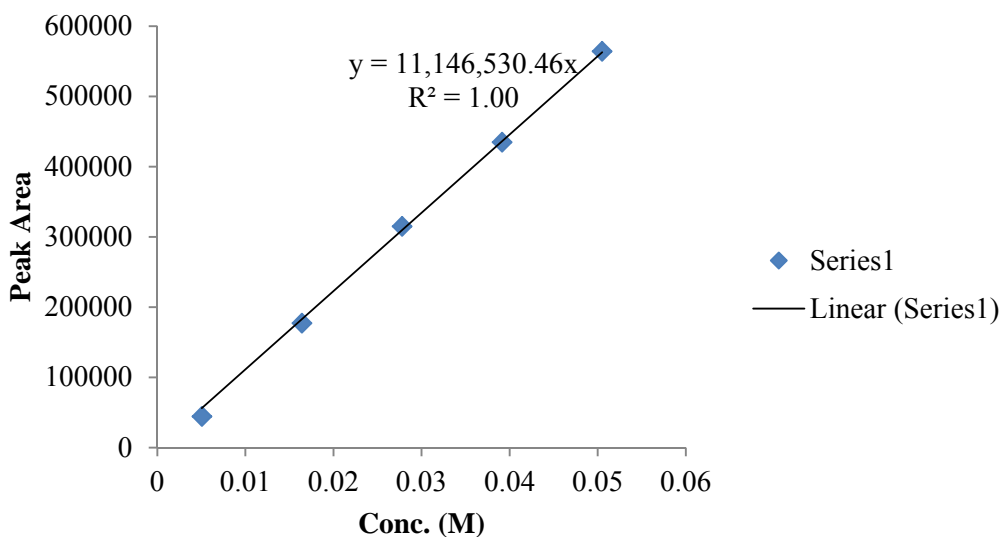
**Figure 3.6. GC-FID Calibration of 5-methyl-2-bromopyridine.**



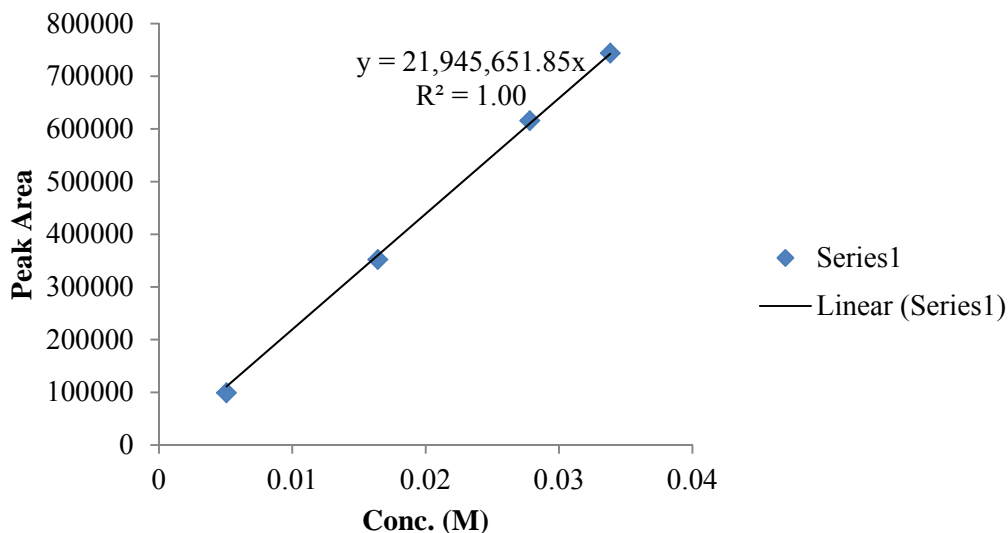
**Figure 3.7. GC-FID calibration of 5-methyl-2-phenylpyridine.**

#### 3.2.2.4 Suzuki Coupling of 4-Amino-2-bromopyridine

4-Amino-2-bromopyridine (16 mmol, 2.7682 g) was added to a 100 mL 3-neck round-bottomed flask along with phenylboronic acid (1.3 eq., 2.5361 g), dipotassium phosphate (3 eq., 8.3616 g), and bis(triphenylphosphine)palladium(II) dichloride (5 mol%, 0.5615 g). The reaction flask was flushed with N<sub>2</sub> for 15 minutes prior to solvent addition. After flushing with inert gas, 30 mL of degassed acetonitrile and 20 mL of degassed H<sub>2</sub>O were added using air-tight syringes. The mixture was then heated to 70 °C and allowed to react for 24 hours with magnetic stirring (90% yield by GC with calibration curve).



**Figure 3.8. GC-FID calibration curve for 4-amino-2-bromopyridine.**



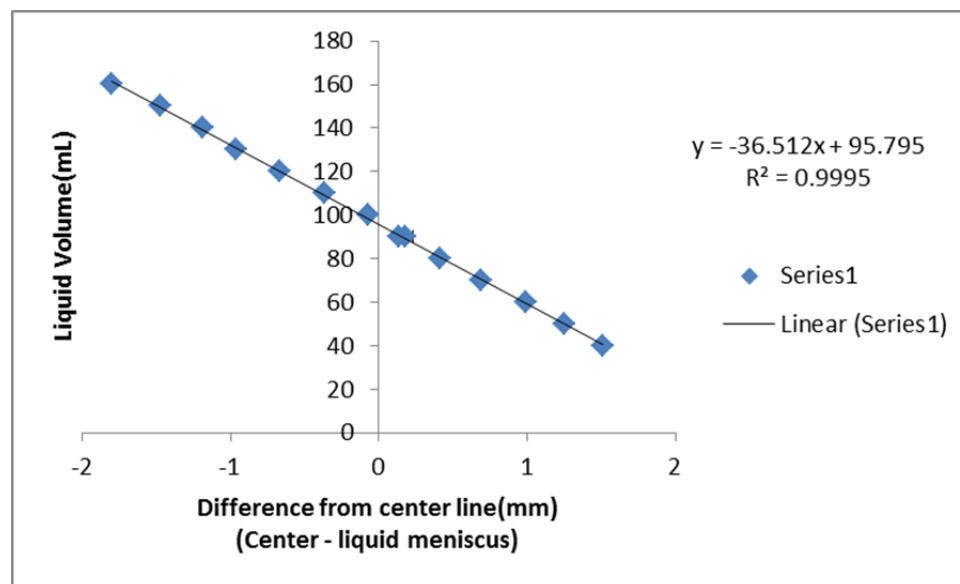
**Figure 3.9. GC-FID calibration curve for 4-amino-2-phenylpyridine.**

#### 3.2.2.5 CO<sub>2</sub>-Induced Separation: Function of Pressure Studies

Suzuki reaction is performed according to the procedure in 3.2.2.3 or 3.2.2.4. After reaction, the salt-rich aqueous phase is decanted using an airtight syringe and replaced with a solution of additive (20 catalyst equivalents, 3.2 mmol) in 20 mL of degassed H<sub>2</sub>O. The mixture is allowed to stir for 15 minutes and is then transferred to a 300 mL Parr bomb reactor (pre-flushed with 1 atm. of CO<sub>2</sub>) equipped with viewing windows. The mixture is then diluted with 42 mL of degassed acetonitrile and 28 mL of H<sub>2</sub>O. The bomb reactor is brought to 100 psig using a 500 mL Teledyne ISCO syringe pump while being stirred mechanically. Once 100 psig is attained, stirring is allowed to continue for 15 minutes (until equilibrium is reached). Following equilibration, stirring is stopped and the mixture is allowed to stand unperturbed for 30 minutes in order to efficiently separate each liquid phase. Prior to sampling, liquid volumes are calculated



using a cathetometer to measure differences in height of the organic meniscus and the organic-aqueous interface compared to that of a calibrated reference point (Figure 3.10).



**Figure 3.10. Height-volume calibration for the cathetometer.**

These differences in heights allow the calculation of the overall ( $V_T$ ) and aqueous phase volumes ( $V_{aq}$ ). The organic volume is then calculated using Equation 3.1.

$$V_{org} = V_T - V_{aq}$$

**Equation 3.1.**

Accurate-volume samples are taken of each phase via dip tube by allowing the phase samples to flow at low velocity through a sample loop of known volume (1.15 mL,  $V_{\text{sample}}$ ) before isolating the sample loop. The isolated sample loop is depressurized and rinsed with acetonitrile (2 mL) and water (1 mL) into a collection vial. The collected sample is then analyzed for organic product content by GC-FID and for palladium content by AAS ( $n_{x,\text{sample}}$ ). With the total sample volume ( $V_{\text{sample}}$ ) and total amount of analyte in the sample ( $n_{x,\text{sample}}$ ,  $x$  = product or palladium) known, Equation 3.2 can be used to calculate the concentration of said analyte under  $\text{CO}_2$  pressure.

$$[x]_{PCO_2} = \frac{n_{x,\text{sample}}}{V_{\text{sample}}}$$

**Equation 3.2.**

With the phase volumes and concentrations under  $\text{CO}_2$  pressure known, the amount of product/palladium can be calculated for each phase and for the entire system using Equation 3.3.

$$n_{x,\text{total}} = [x]_{\text{aq}} V_{\text{aq}} + [x]_{\text{org}} V_{\text{org}}$$

**Equation 3.3. Calculation of total amount of analyte (x) under  $\text{CO}_2$  pressure.  $x$  = Pd or reaction product.  $[x]$  is concentration under  $\text{CO}_2$  pressure.  $V$  = volume under  $\text{CO}_2$  pressure.**

After organic and aqueous samples are collected, pressure on the system is increased and the above procedure is followed for 200 psig and 400 psig measurements.

#### *3.2.2.6 CO<sub>2</sub>-Induced Separation: Combinatorial Apparatus*

Additive screening was conducted under 200 psig of CO<sub>2</sub> pressure using a custom-built, multi-sample apparatus composed of eight 3-mL titanium mini-reactors and a gas supply manifold able to deliver uniform pressures to each cell (Figure 3.4). Suzuki reaction is performed according to the procedure in 3.2.2.3 or 3.2.2.4. Following reaction, the aqueous phase of the reaction system is removed. 1.0mL aliquots of the palladium-rich organic phase were transferred via airtight syringe to vials under inert gas where the samples were treated with solutions of 20 equivalents of specified additive in 1.6mL degassed water and 1.4mL degassed ACN. Once mixed, the solutions were transferred via airtight syringe to individual cells, pressurized to 200 psig CO<sub>2</sub>, and samples of known volume were obtained via dip tube to determine organic and aqueous phase palladium (AA analysis) and product (GC analysis) concentrations. Phase volumes and organic phase expansion under CO<sub>2</sub> pressure were estimated based upon previous phase volume measurements under CO<sub>2</sub> pressure using the apparatus in Figure 3.5. With palladium/product concentrations and phase volumes known, the amount of aqueous and organic palladium and reaction product can then be determined.

#### *3.2.2.7 CO<sub>2</sub>-Induced Separation: Total Decant Studies*

For total decant experiments, the same procedure described in 3.2.2.5 is used to transfer post-reaction material to the Parr bomb reactor. Once the mixture has been transferred to the bomb reactor and diluted, the reactor is pressurized to the desired pressure via syringe pump and allowed to equilibrate with stirring for 30 minutes. Once

equilibrium is reached, stirring is stopped and the mixture is allowed to stand unperturbed overnight to allow clear and distinct phase separation. After phase separation, the aqueous phase is removed at pressure using a dip tube positioned for full solvent recovery. Volumes of the depressurized aqueous and organic phases are recorded and each sample is measured for palladium and product content. After analysis, the aqueous phase is optionally treated with activated carbon (20 g/L) and stirred as a slurry for 24 hours. Solid carbon was removed via gravity filtration and the remaining aqueous phase was measured for palladium content.

### 3.2.3 Instrumentation

Palladium concentration was measured using a Shimadzu AA-7000F Atomic Absorption Spectrometer, measuring at 244.7 nm. Background noise was removed from signal by self-reversal, with a current swing of 10 mA – 300 mA. Analysis occurred at a fuel gas flow rate of 1.8 l/min and an air flow rate of 15 l/min. Calibration curves were prepared by dissolving known amounts of bis(benzonitrile)palladium(II) dichloride into a 0.4% solution of (poly)ethyleneimine in 60/40 MeCN/H<sub>2</sub>O. Samples for analysis were dissolved in a 0.4% solution of (poly)ethyleneimine in 60/40 MeCN/H<sub>2</sub>O.

Concentrations of reaction substrates and products were measured using a Shimadzu GC-FID with calibration curves dissolved in 60/40 MeCN/H<sub>2</sub>O. Samples were diluted in ACN to concentrations which fell within calibration curves. The GC-FID methods used an initial and final oven temperature of 195 °C and 320 °C and a gradient of 15 °C. Calibration curves of reaction products and reactants are shown in 4.2.2.

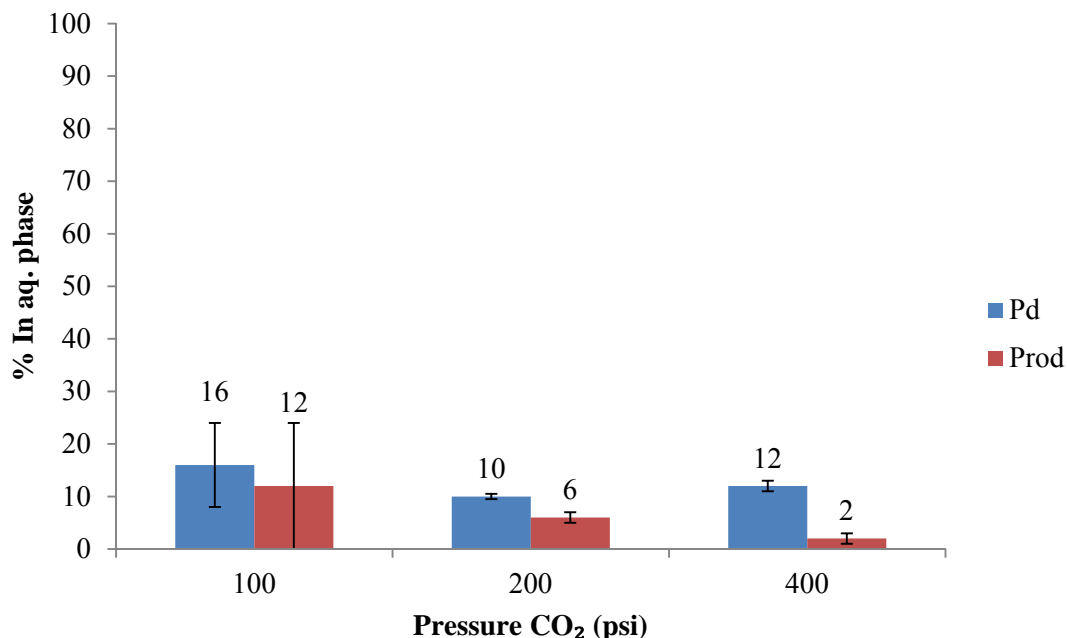
### 3.3 Results and Discussion

#### 3.3.1 2-Bromo-5-methylpyridine

##### *3.3.1.1 Baseline Separation*

In order to determine a baseline for separation studies, separations were performed following the reaction of 2-bromo-5-methylpyridine (3.2.2.3/Scheme 3.1) according to the process in 3.2.2.5/Figure 3.2. These separations used no additive and were performed at pressures of 100, 200, and 400psi.

Figure 3.11 shows the amount of aqueous Pd and product obtained during baseline separation trials. At 100, 200 and 400psi pressure of CO<sub>2</sub>, 16%, 10%, and 12% of Pd and 12%, 6%, and 2% of product are present in the aqueous phase. The product and palladium partitioning results indicate strong hydrophobicity of both compounds under these separation conditions. Considering the aromatic nature of the product, its partitioning results are not surprising. The behavior of the catalyst is an indication that the palladium is likely coordinated with the hydrophobic product, hydrophobic phosphine ligand, or both. Additionally, the fact that the aqueous amounts of Pd and reaction product remain relatively constant as a function of CO<sub>2</sub> pressure (differences of 4% and 8% for Pd and product from 100 to 400psi), indicate that CO<sub>2</sub> pressure does not have a large effect on the separation for the conditions studied.



**Figure 3.11. Baselined separation results as a function of CO<sub>2</sub> pressure. Prod = 5-methyl-2-phenylpyridine.**

The key implication of the separation results seen in Figure 3.11 is that, since the reaction product demonstrates hydrophobicity and potentially coordinates with catalyst (making the palladium hydrophobic under these conditions), additives must be selected that will both coordinate with the Pd catalyst and make the Pd more hydrophilic. In order to effectively manipulate the hydrophilicity of palladium under application of CO<sub>2</sub>, a variety of additives were screened as possible palladium chelants. The results of these studies are summarized in section 3.3.1.2.

### 3.3.1.2 Additive screening

Additive screening to evaluate Pd separation from 5-methyl-2-phenylpyridine was conducted under 200 psi of CO<sub>2</sub> pressure using the procedure in 3.2.2.6 after performing the Suzuki reaction described in 3.2.2.3/Scheme 3.1.

Among the classes of compounds screened are: amino acids, guanidines, phosphines, polyamines, polyacids, thiols, pyridines, ionic salts and acidic compounds (

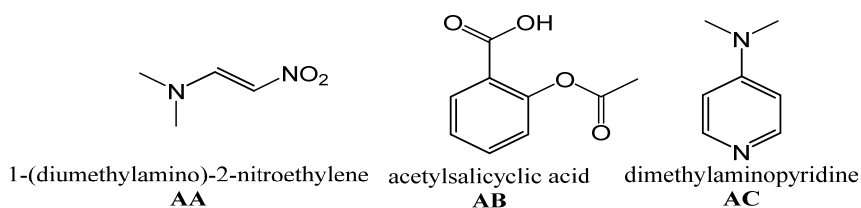
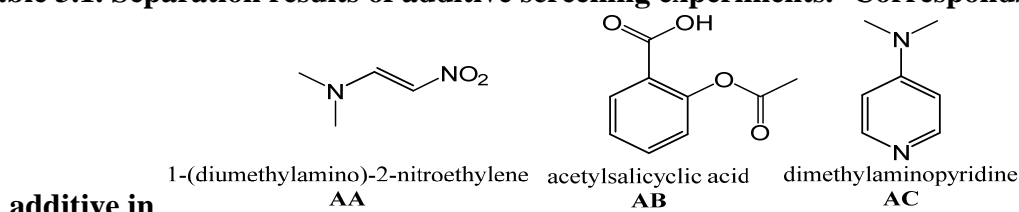


Figure 3.3). These additives were chosen based on their ability to chelate/bind with CO<sub>2</sub> and based on their anticipated hydrophilicity under separation conditions. The results of the additive screening are shown in Table 3.1.

**Table 3.1. Separation results of additive screening experiments. <sup>1</sup>Corresponds to**



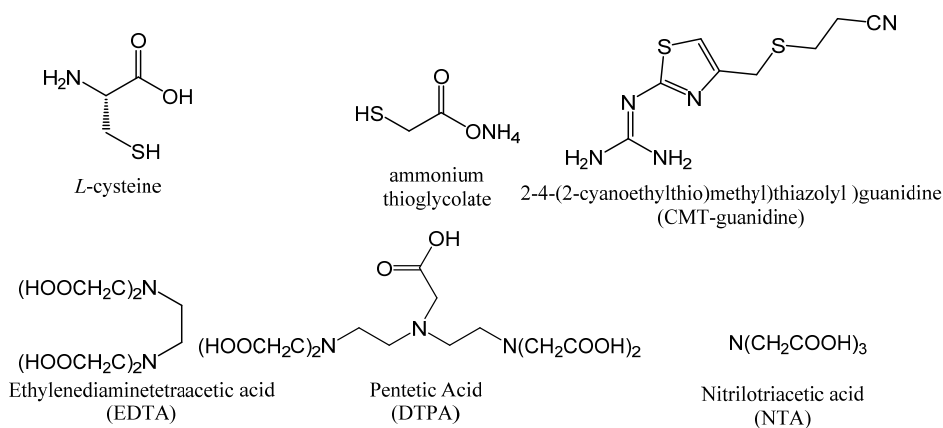
**Figure 3.3. <sup>2</sup>5-methyl-2phenylpyridine.**

Additive <sup>1</sup>	% Pd in Aqueous Phase	%Prod <sup>2</sup> . in aqueous phase
A	75±5	5±1
B	19 ±1	2±0
C	10	1.5

D	29	1
E	9	2
F	45	1
G	0	2
H	62±0	10±1
I	36±4	2±0
J	69±1	1±0
K	9	2
L	47±2	3±1
M	2	1
N	5	2
O	39±1	2±0
P	23±2	5
Q	5	2
R	36±1	4±2
S	24	1
T	5	1
U	8±1	3±0
V	54±4	1±0
W	63	10
X	55±15	22±4
Y	54	1
Z	53	59
AA	24±2	1±1
AB	14±1	2
AC	10	2

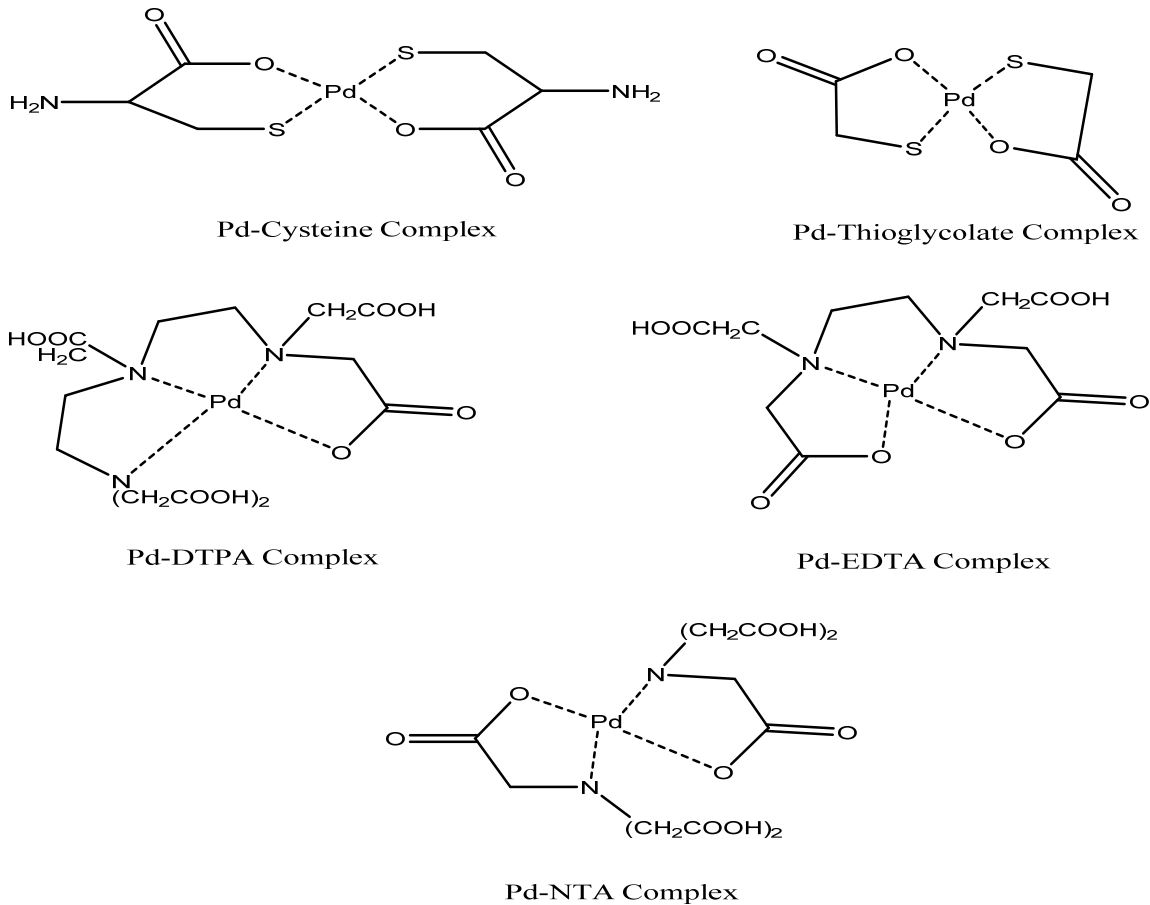


Table 3.1 shows varying levels of successful Pd separation from reaction product with aqueous Pd values ranging from 0% to 75%. From the additives screened, those which demonstrate the most successful separation of Pd from reaction product are shown in Figure 3.12.



**Figure 3.12. Top Additives Screened for Separation of Pd from 5-methyl-2-phenylpyridine.**<sup>29-32</sup>

The additives seen in Figure 3.12 are made up of two main additive classes. Cysteine, ammonium thioglycolate, and CMT-guanidine, are all sulfur-containing additives with multiple basic sites which could result in chelation with the palladium.<sup>29-30</sup> EDTA, DTPA, and nitrilotriacetic acid are all polyacids with no sulfur present. Despite the lack of sulfur, these polyacids all contain multiple sites which could bind with palladium, thus offering the potential for chelation.<sup>31-32</sup> Figure 3.13 shows some structures which have been proposed in literature

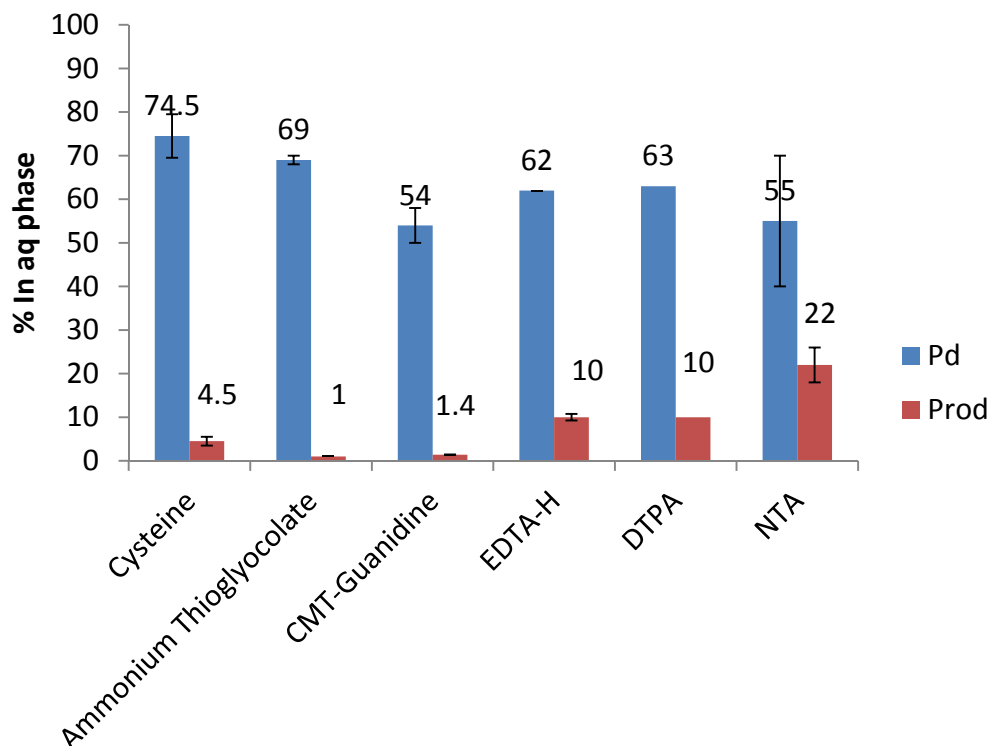


**Figure 3.13. Pd-chelant structures from literature.**

Additionally, all of these additives are hydrophilic in nature. The octanol-water partitioning coefficient ( $K_{ow}$ ) of an additive is a good estimation of the additive's partitioning in the OATS system between a polar, protic solvent (water) and a less polar, aprotic solvent (such as CO<sub>2</sub>-expanded acetonitrile). The  $K_{ow}$ 's of the additives in Figure 3.12 are approximately 0.003 for cysteine, CMT-guanidine, EDTA, DTPA, and NTA and 0.001 for ammonium thioglycolate.<sup>33-36</sup> The partitioning of the additives serves as an

approximation for how they might influence the hydrophilicity of Pd if bound to the catalyst. The results of these separations are seen in Figure 3.14.

Figure 3.14 shows that <5% of reaction product is found in the aqueous phase for the separations using cysteine, ammonium thioglycolate, and CMT-guanidine. These results are consistent with the amount of aqueous product seen in baseline separations at 200psi of CO<sub>2</sub> pressure (6%). EDTA, DTPA, and NTA give aqueous product amounts of 10%, 10%, and 22%, all slightly higher amounts than seen in the baseline separation. The polyacids are significantly more acidic ( $pK_{a1} = 2.23, 1.8$  and  $1.89$  for EDTA, DTPA, and NTA) than the sulfur compounds examined ( $pK_{a1} = 8.51$ , and  $9.9$  for CMT-guanidine and ammonium thioglycolate, cysteine has sites with  $pK_a$ 's of  $8.2, 2.1, 11$ ). This increased hydrophilicity seen with these additives indicates that the acidity of the additive used may play a role in the hydrophilicity of the product during separation.



**Figure 3.14. Separation results of selected additives**

As Figure 3.14 shows, cysteine, ammonium thioglycolate, CMT-Guanidine, EDTA, DTPA, and NTA give 75%, 69%, 54%, 62%, 63%, and 55% of soluble palladium in the aqueous phase at 200psi CO<sub>2</sub>. These values are all significantly higher than the amount of aqueous palladium seen when no additive is used at the same pressure of CO<sub>2</sub> (10% Pd). This result demonstrates that separation of Pd from Suzuki reaction product is achievable with OATS technology through careful additive selection, for additive selection is crucial to influencing Pd hydrophilicity in the OATS separation. Given that all the additives in Figure 3.14 have roughly the same hydrophilicity, their differences in performance likely stem from chelation ability. The two most effective additives, cysteine and ammonium thioglycolate, both contain sulfur and have geometries which

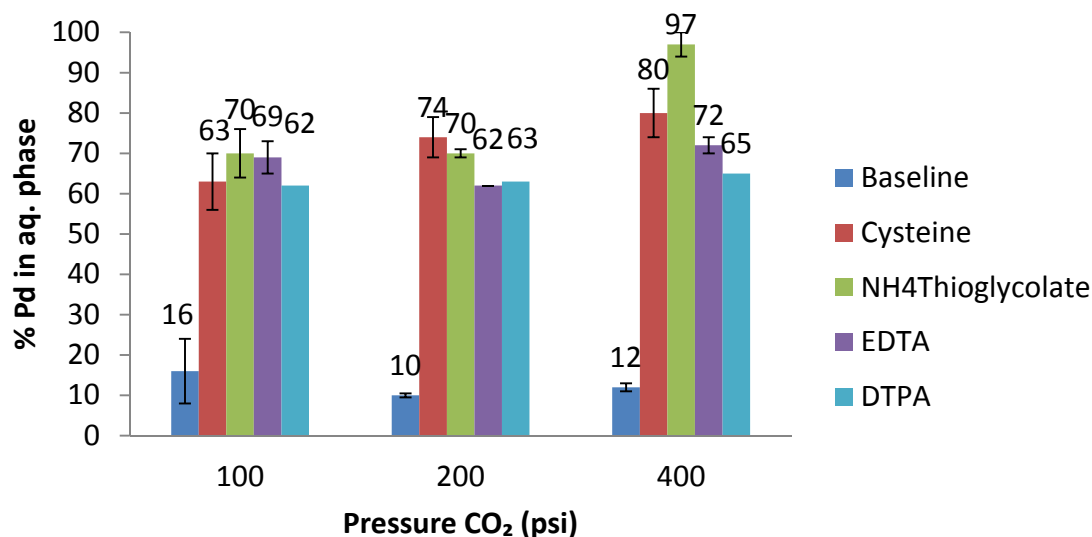
readily enable Pd chelation with a corresponding oxygen atom<sup>29,37-38</sup>. CMT-guanidine contains sulfur and has the geometry to form a bidentate complex with its sulfur and cyano moieties or between nitrogen sites and the CN moiety; however, cyano groups are not considered to bind as strongly to Pd. Thus, CMT-guanidine is likely not as strong of a chelant and gives a lower amount (54%) of aqueous palladium. The performance of the polyacids (EDTA, DTPA, NTA) can also be explained by their ability to chelate. EDTA, DTPA, and NTA all contain multiple nitrogen and oxygen atoms capable of coordinating with Pd, thus these compounds can readily chelate with palladium and move it into the aqueous phase<sup>31-32,39-40</sup>.

#### *3.3.1.3 Effect of CO<sub>2</sub> Pressure*

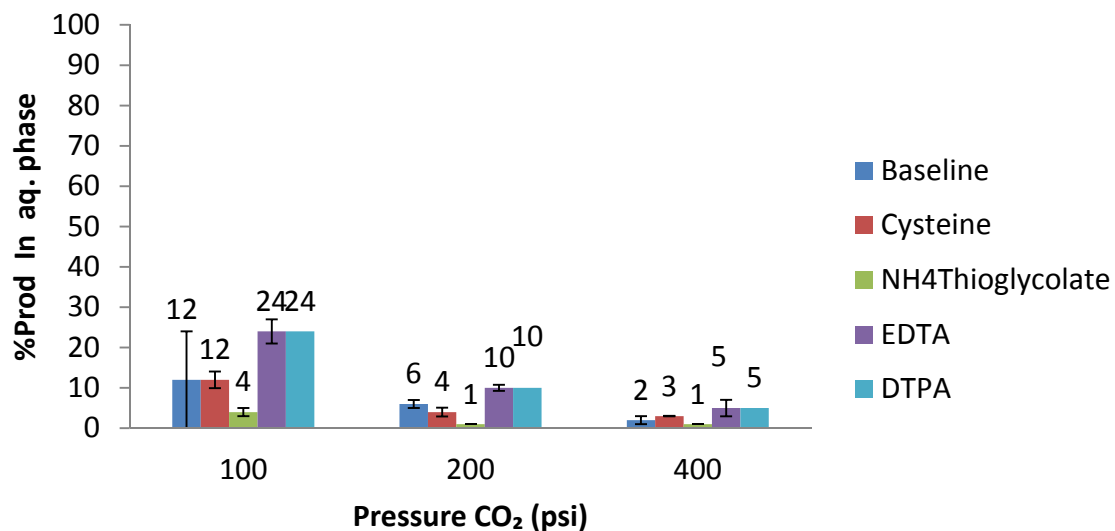
Having established successful separation of Pd using OATS technology at 200psi, it was important to understand how the separation varies as a function of CO<sub>2</sub> pressure. Pressure is a key parameter in vessel design cost, thus, it is more desirable to obtain good separation at lower CO<sub>2</sub> pressures. However, previous work shows that as CO<sub>2</sub> pressure is lowered in an ACN/H<sub>2</sub>O system, the fraction of water in the ACN-rich phase increases and the kamlett-taft parameter of the ACN-rich phase increases as well, making the phase more polar.<sup>22</sup> Thus, too little CO<sub>2</sub> pressure could hurt separation of Pd from product. To test the effect of CO<sub>2</sub> pressure, separations using two sulfur additives (cysteine and ammonium thioglycolate) and two polyacid additives (EDTA and DTPA) were studied as a function of CO<sub>2</sub> pressure. Experiments were performed using the apparatus in Figure 3.5 according to the process described in 3.2.2.5.

Figure 3.15 and Figure 3.16 summarize the aqueous-phase palladium and reaction product content of the selected additives at 100, 200, and 400 psi of CO<sub>2</sub>. The baseline

case in which no additives are employed is also shown. At 100psi CO<sub>2</sub> pressure, cysteine, thioglycolate, EDTA, and DTPA give 63%, 70%, 69%, and 62% of palladium and 12%, 4%, 24%, 24% of product in the aqueous phase. The aqueous palladium amounts are significantly higher than the 16% palladium found when no additive is used. When either of the two sulfur additives are used, the amount of product present in the aqueous phase is less than or equal to the amount of aqueous product (16%) in the baseline case. The two polyacids give slightly higher amounts of aqueous product at 100psi CO<sub>2</sub>. This result agrees with the trend seen previously where the acidity of the additive made the reaction product more hydrophilic under OATS conditions. Despite this, at 100psi CO<sub>2</sub>, all of the additives examined give significantly better separation than the baseline experiment.



**Figure 3.15. Aqueous phase palladium content as a function of CO<sub>2</sub> pressure. Pd % is normalized for Pd in solution.**



**Figure 3.16. Aqueous product content as a function of CO<sub>2</sub> pressure.**

At 200psi CO<sub>2</sub>, these same additives give 74%, 70%, 62%, and 63% of palladium and 4%, 1%, 10%, 10% of product in the aqueous phase. None of these aqueous palladium amounts, aside from cysteine, at 200psi CO<sub>2</sub> represent a significant change in palladium content from the 100psi CO<sub>2</sub> separation. However, the aqueous product results are all lower in 200psi separations than in 100psi separations, particular in the case of EDTA and DTPA, so while the amount of aqueous palladium is unchanged, the separation is improved, for more product remains in the organic phase.

At 400psi CO<sub>2</sub>, cysteine, thioglycolate, EDTA, and DTPA give 80%, 97%, 72%, and 65% of palladium and 3%, 1%, 5%, 5% of product in the aqueous phase. The amount of aqueous palladium for separations using cysteine, thioglycolate, and EDTA is higher compared to separations under 100 and 200psi of CO<sub>2</sub>. Additionally, the amount of product in the aqueous phase is the lowest for all of these additives at 400psi CO<sub>2</sub>. Thus,

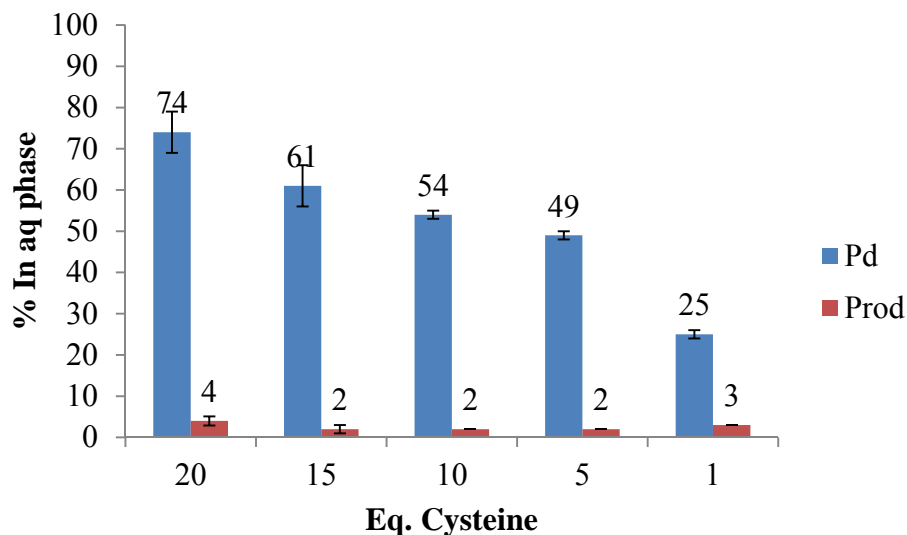
it can be said that for each of the additives examined, the separation of Pd from reaction product improves with increasing CO<sub>2</sub> pressure.

While ammonium thioglycolate obtains the highest amount of aqueous Pd (97%), it is important to note the phase behavior observations made during this study. During separations at 400 psi of CO<sub>2</sub> pressure, a significant amount of solid precipitates. When these solids are present, 52% of total palladium is unaccounted for within the liquid phases suggesting that palladium is precipitating or co-precipitating with these solids. Palladium precipitation is also confirmed via AAS analysis of the isolated solids. While the solid Pd is still effectively separated from reaction product (negligible amounts of reaction product are found in the solid), the presence of the solids presents processing difficulties. As a result, cysteine (80% aqueous palladium at 400psi) was chosen as the optimum additive for Pd separation using OATS technology.

#### *3.3.1.4 Effect of Cysteine Loading*

As a means of understanding whether the amount of cysteine could be reduced in this OATS separation, separations were performed at 200 psi using the apparatus in Figure 3.4 with varied amounts of cysteine using the procedure in 3.2.2.6. The results are given in Figure 3.17.





**Figure 3.17. Aqueous Phase Palladium Retention as a Function of Cysteine Loading**

The experiments performed at 200 psi CO<sub>2</sub> pressure with 15, 10, 5, and 1eq of cysteine (compared to Pd) give 61%, 54%, 49%, and 25% of palladium in the aqueous phase and 4%, 2%, 2%, 2%, and 3% of aqueous product. A small change is seen when increasing from no cysteine (10% aqueous palladium) to one catalyst equivalent of cysteine (25% total palladium removal), relative to the catalyst concentration. However, aqueous palladium retention is greatly increased as the amount of cysteine present is elevated, increasing from approximately 50% using 5 equivalents of cysteine to 74% using 20 equivalents of cysteine. The aqueous reaction product amount is relatively unchanged regardless of the amount of cysteine used. The results in Figure 3.17 indicate the there is a significant loss in separation performance when the cysteine loading is decreased from 20eq. of Pd.

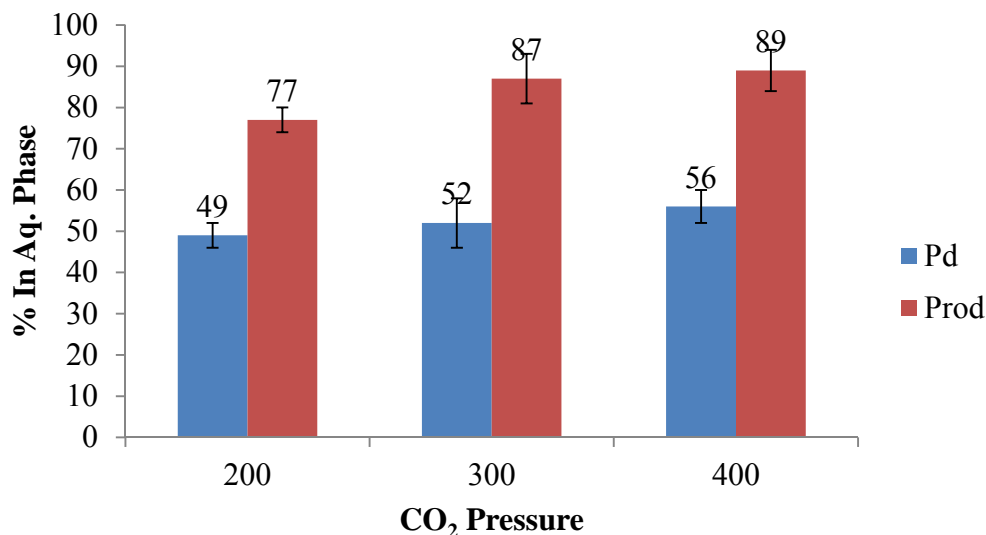
In order to fully demonstrate the economic advantage of OATS palladium removal and recovery, separations were conducted with cysteine in which the total aqueous phase was decanted at 400 psi CO<sub>2</sub> and treated with activated carbon, thereby eliminating the production of a large, palladium-rich aqueous waste stream. Following separation, the palladium-rich aqueous phase was treated with activated carbon (20 g/L). It was found that, despite the presence of cysteine, effectively all of the separated palladium was able to be recovered via treatment with activated carbon. It was therefore observed that the OATS separation process coupled with activated carbon can provide a facile palladium removal procedure in which 80% of process catalyst can be removed from an organic, product-rich stream without the generation of high-volume aqueous waste stream, all with the addition of easily-removed CO<sub>2</sub> and relatively inexpensive additive

### 3.3.2 4-Amino-2-bromopyridine

In order to probe the versatility of this technique, OATS technology was also used to attempt separation of Pd from 4-amino-2-phenylpyridine (product of reaction in Scheme 3.2).

Suzuki coupling reaction to produce this product was performed using the procedure in 3.2.2.4/Scheme 3.2 to couple 4-amino-2-phenylpyridine with phenylboronic acid using TPP as a ligand, K<sub>2</sub>HPO<sub>4</sub> as a base, and a water/ACN solvent system.

Following reaction, separation was performed following the process in 3.2.2.5/Figure 3.2 with no additive to establish a baseline for Pd separation as a function of CO<sub>2</sub> pressure. The results are shown in Figure 3.18.

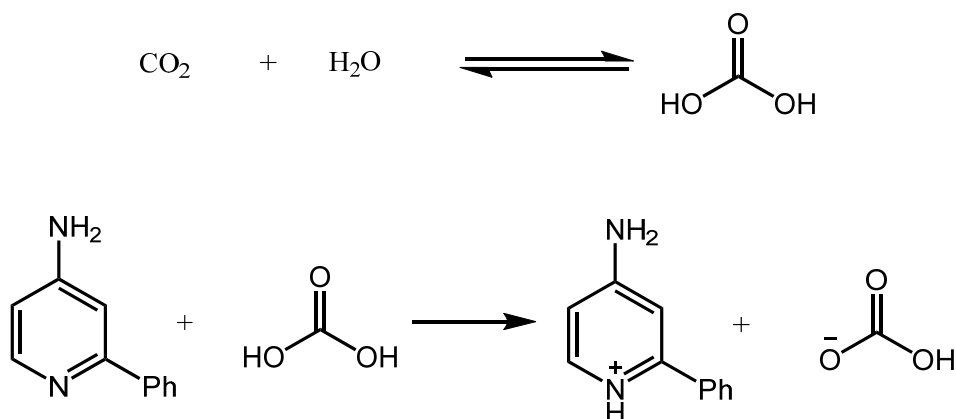


**Figure 3.18. Separation of Pd from 4-amino-2-phenylpyridine as a Function of CO<sub>2</sub> pressure.**

At 200, 300, and 400psi of CO<sub>2</sub>, the amount of aqueous Pd is 49%, 52% and 56%. At these same pressures, the amount of aqueous product is 77%, 87%, and 89%. Interestingly, there is a higher amount of palladium in the aqueous phase when 4-amino-2-phenylpyridine is used compared to 5-methyl-2-phenylpyridine (49% compared to 10% at 200 psi). As the pressure increases, there is not a large change in the amount of aqueous Pd (7% from 200 to 400psi) when no additive is used. Additionally, the amount of aqueous reaction product is much higher than in the case of the 5-methyl-2-phenylpyridine system (77% compared to 6% at 200psi), and, similar to the amount of aqueous Pd, the amount of aqueous product also shows a slight increase (12%) from 200psi to 400psi.

The increased hydrophilicity of 4-amino-2-phenylpyridine (compared to 5-methyl-2-phenylpyridine) in this system is likely explained by protonation of the 4-

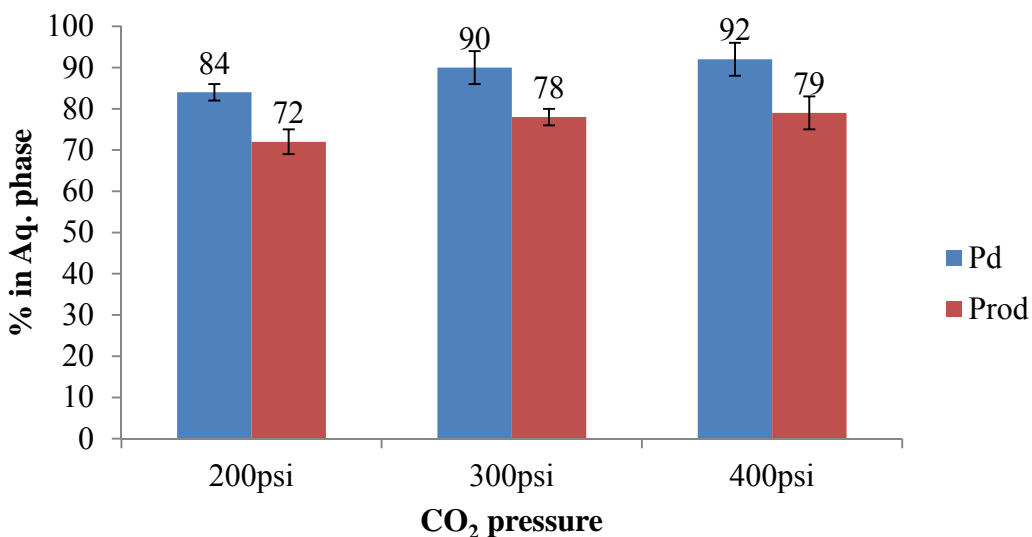
amino-2-phenylpyridine in the presence of carbonic acid produced by the absorption of CO<sub>2</sub> into the aqueous phase. A proposed reaction scheme is shown in Figure 3.19.



**Figure 3.19. Formation of Carbonic Acid via CO<sub>2</sub> Addition to Water and Subsequent Proton Exchange with 4-amino-2-phenylpyridine.**

Water reacts with CO<sub>2</sub> added to the system to form carbonic acid, increasing the acidity of the separation under CO<sub>2</sub> pressure. While this acid is present in both systems (4-amino-2-phenylpyridine and 5-methyl-2-phenylpyridine), the amino substrate has  $\pi$ -donation into its ring from the amino group, making the substrate more basic than the 5-methyl counterpart. This increased basicity leads to a higher degree of protonation, generating an ionic species that would be expected to have an increased solubility in water. Additionally, the protonated product is unlikely to coordinate with Pd. This could explain why more Pd exists in the aqueous phase than in the baseline case when 5-methyl-2-phenylpyridine is present (Figure 3.11).

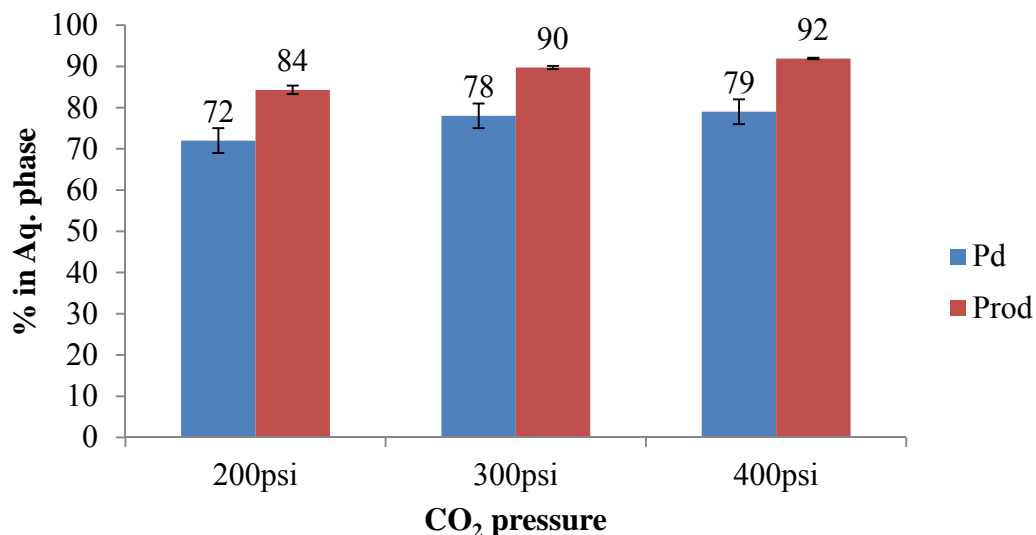
Both cysteine and thiourea were used as additives as a means of enhancing the separation of catalyst from 4-amino-2-phenylpyridine following Suzuki reaction. Following the procedure in 3.2.2.5/Figure 3.2, separations were studied as a function of CO<sub>2</sub> pressure. The results are shown in Figure 3.20 and Figure 3.21.



**Figure 3.20: Separation data of Pd from 4-amino-2-phenylpyridine using Cysteine as additive. Function of CO<sub>2</sub> pressure. Prod: 4-amino-2-phenylpyridine.**

Separations under CO<sub>2</sub> pressure using cysteine as an additive give 84%, 90%, and 92% Pd and 72%, 78%, and 79% reaction product in the aqueous phase (Figure 3.20). The cysteine is effective in increasing the amount of aqueous Pd compared to the baseline case (Figure 3.18: 49%, 52%, and 56% at 200, 300, and 400psi CO<sub>2</sub>). This increase in aqueous Pd is likely a result of chelation of the hydrophilic cysteine additive with the Pd. The amount of aqueous reaction product is slightly lower compared to the baseline case

(Figure 3.18: 77%, 87%, 89% at 200, 300, and 400psi); however, the high amount of product in the aqueous phase makes the separation ineffective.



**Figure 3.21. Separation data of Pd from 4-amino-2-phenylpyridine using thiourea as additive. Function of CO<sub>2</sub> pressure. Prod: 4-amino-2-phenylpyridine.**

Separations using thiourea (Figure 3.21) give 72%, 78%, and 79% of Pd and 84%, 90%, and 92% of product in the aqueous phase. The amounts of aqueous Pd are once again higher than when no additive is used, a result of sulfur's ability to strongly bind with the Pd catalyst. Unfortunately, the amount of product in the aqueous phase is still too high for the separation to be considered effective.

### 3.4 Conclusions

The use of Organic/Aqueous Tunable Solvents in conjunction with careful additive selection has been found to be an effective method for the removal of homogeneous palladium from the Suzuki coupling reaction product 5-methyl-2-phenylpyridine. Among those screened, cysteine, ammonium thioglycolate, CMT-guanidine, EDTA, DTPA, and NTA all stand out as effective additives for separating Pd from reaction product. At 400psi CO<sub>2</sub> pressure, these additives give >60% of Pd and <5% reaction product in the aqueous phase. This work has also shown that over a range of 100 to 400psi, as CO<sub>2</sub> pressure increases, aqueous Pd increases and aqueous product decreases. With cysteine, a dependence of palladium removal on additive loading has also been demonstrated, varying from 10% palladium removal with no cysteine to 74% palladium removal when 20 equivalents are used under 200 psi of CO<sub>2</sub>. Finally, the ability of activated carbon to extract the palladium from the catalyst-rich aqueous phase has been demonstrated, highlighting the capability of this process to be immediately implemented into existing technologies in a manner that adheres to the principles of green chemistry and engineering.

An investigation into substrate scope expansion through the separation of Pd from 4-amino-2-phenyl pyridine also provided interesting results. The use of cysteine and thiourea in 4-amino-2-phenylpyridine systems exhibits the ability to increase the amount of palladium in the aqueous phase (92% and 79% at 400psi) compared to the baseline (56% at 400psi). However, a large percentage of product is found in the aqueous phase (79%, 92%, and 89% with cysteine, thiourea, and no additive at 400psi) preventing successful separation. It is conjectured that carbonic acid formed under CO<sub>2</sub> pressure,

leads to protonation of the reaction product. This revealed an important limitation in this technology: separation of Pd into the aqueous phase from more basic N-containing heterocycles may be difficult due to increased reaction product hydrophilicity under OATS conditions.



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## CHAPTER 4 - RECYCLE OF PALLADIUM USING SMART SOLVENTS

### 4.1 Introduction

#### 4.1.1 Suzuki Coupling

Heterocyclic biaryl compounds, particularly those containing nitrogen, are components in many pharmaceutical and biologically active molecules. Consequently, these molecules represent important synthetic targets.<sup>1-4</sup> Carbon-carbon bond formation between aromatic compounds is often a key step in the synthesis of these synthetic targets. The Suzuki coupling reaction (Figure 3.1), a metal-catalyzed coupling of an organoboronic acid/ester with an organic halide, has emerged as ubiquitous means of forming these bonds.<sup>5-6</sup> This reaction is desirable, for its use of relatively safe and easily accessible reagents, facile reaction conditions and tolerance of a wide range of functional groups on reaction substrates.<sup>7</sup>

#### 4.1.2 Catalyst Separation and Recycle Motivation

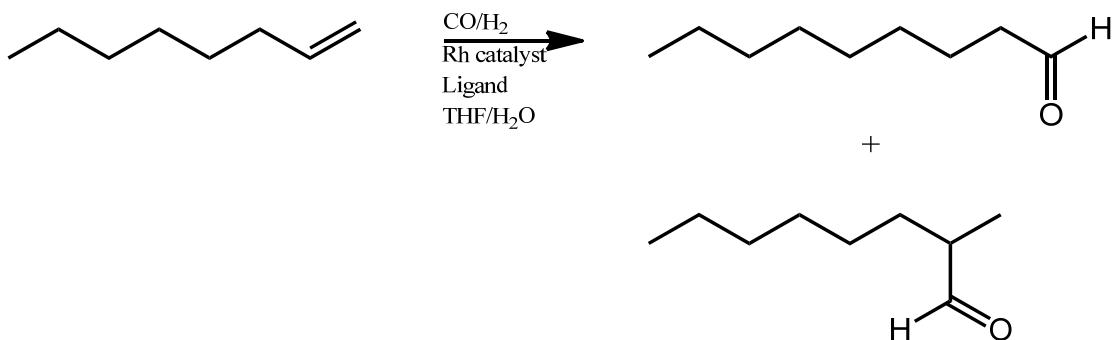
Palladium is an effective catalyst for Suzuki coupling reactions; however, federal regulations limit the amount which may be present in pharmaceutical and agriculture compounds; as a result, separation of the catalyst from reaction product is a key process step.<sup>8</sup> Additionally, palladium is an expensive metal and successful recycle of Pd catalyst following separation offers the potential for large cost-savings within processes that use the Suzuki coupling reaction.<sup>9</sup>

Homogenous palladium, while offering superior reaction rates compared to heterogeneous catalysis, results in a more difficult separation from reaction product.<sup>10</sup> The presence of heteroaromatic compounds (the components of the synthetic targets discussed earlier) in solution offers additional challenges, for these compounds are known to coordinate with palladium and make separation more difficult. Many examples of post-reaction palladium separation and recycle exist; however, these techniques use expensive ligands (expensive phosphine ligands), solvents (halogenated, ionic liquids), or do not involve separation from coordinating reaction products.<sup>11-13,2</sup> Additionally, it is known that a buildup of inorganic salts following reaction can limit subsequent recycle reactions.<sup>14-15</sup> A technique which could achieve effective separation and recycle of palladium from a coordinating Suzuki reaction product, while using inexpensive ligands, inexpensive solvents and preventing the build-up of inorganic salts would prove to be very desirable from an industrial perspective. The use of organic/aqueous tunable solvents (OATS) or an inexpensive anti-solvent such as toluene offer opportunities to achieve such a process<sup>16-17</sup>.

#### 4.1.3 OATS

OATS consists of ternary solvent systems comprised of water, a water-miscible organic solvent and an anti-solvent gas (water/THF/CO<sub>2</sub> or water/acetonitrile/CO<sub>2</sub> are two examples). The solvent system remains homogeneous under inert/air until CO<sub>2</sub> pressure is applied. The organic solvent preferentially absorbs CO<sub>2</sub> and causes a phase split. The phase split results in an aqueous-rich phase containing negligible amounts of CO<sub>2</sub> and an organic-rich gas-expanded liquid layer. As a result, OATS offers the ability to conduct homogeneous reactions (under air/inert gas) and heterogeneous separations

(under CO<sub>2</sub> pressure). An example of an OATS process is shown by Hallet *et al*, wherein hydrophilic catalyst is recovered from the homogeneous hydroformylation reaction of octene in THF/H<sub>2</sub>O using moderate pressures of CO<sub>2</sub>.<sup>18</sup>



**Figure 4.1. Rhodium-Catalyzed Hydroformylation of 1-octene**

Similarly, Chapter 3 demonstrates that OATS technology, combined with careful additive selection, can achieve effective separation of Pd from organic reaction product following Suzuki reaction.

An advantage of using OATS technology is that CO<sub>2</sub> is easily removed through depressurization of the system. The downside of this technology is that the higher CO<sub>2</sub> pressures often required can necessitate costly reactor design considerations. A potential solution is the use of toluene as an anti-solvent. Toluene would induce a phase split following reaction and avoid the use of higher pressure; however, removal of the toluene would be more difficult.

This work establishes a novel method for the recovery and recycle of homogeneous palladium catalyst from post-Suzuki reaction mixtures containing coordinating products, while using inexpensive ligands, solvents, and additives. It also eliminates the build-up of inorganic salts between reactions. The process described in this work achieves these goals by using either organic aqueous tunable solvents (OATS) or an organic cosolvent (toluene) coupled with a “sacrificial additive” to separate palladium catalyst from organic reaction product following a palladium-triphenylphosphine catalyzed Suzuki coupling reaction. The term sacrificial additive is used to describe an inexpensive compound added following Suzuki reaction to influence the phase partitioning of said catalyst for separation from the Suzuki coupling product. This additive is not recycled throughout the process and needs fresh addition for every separation. Following separation using this additive, the catalyst retains its activity and allows further Suzuki chemistry to be achieved.

The primary reaction studied (Scheme 4.1) is the Suzuki coupling of 5-methyl-2-bromopyridine with phenylboronic acid using a palladium-triphenylphosphine catalyst to give 5-methyl-2-phenylpyridine. Through the study of this substrate, the choice of sacrificial additive, pH of the separation system, amount of solvent added, and the use of a “wash step” are all found to be key parameters in the separation of palladium from reaction product. The amount of base and TPP ligand added to prior to recycle reaction are found to be key parameters for successful recycle of Pd separated from this system.

In addition to the system above, the separation and recycle of palladium from several other Suzuki pyridine products were examined. The results from these studies indicate that the basicity of the reaction product and the pH of the separation system play key

roles in successful separation of Pd from reaction product. The detailed results are discussed herein.

## 4.2 Experimental

### 4.2.1 Materials

Deionized water was prepared in-house and used throughout the course of the described experiments. Before use, the water was degassed by sparging with N<sub>2</sub> for 30 minutes. Acetonitrile was purchased from VWR and degassed by N<sub>2</sub> sparge before use. Bis(triphenylphosphine)palladium(II) dichloride, palladium chloride, potassium phosphate, triphenylphosphine, and phenylboronic acid were purchased from Sigma-Aldrich and used as received. 2-bromo-5-methylpyridine was purchased from Matrix Scientific and used as received. 4-amino-2-bromopyridine, 6-amino-2-bromopyridine, and 4-bromoanisole were purchased from Sigma-Aldrich and used as received. Throughout the course of this study, many additives were purchased from commercial chemical suppliers and used as received. N<sub>2</sub> and SFE-grade CO<sub>2</sub> was purchased from Airgas and used as received.

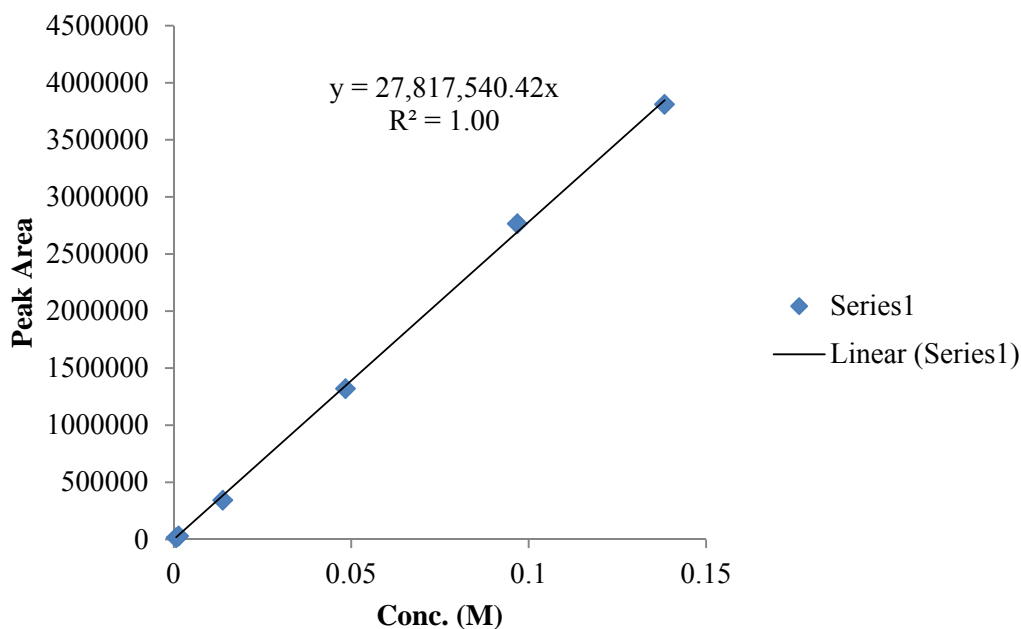
### 4.2.2 Experimental

#### 4.2.2.1 *Suzuki Coupling of 2-Bromo-5-methylpyridine*

2-bromo-5-methylpyridine (16 mmol, 2.7523 g) was added to a 100 mL 3-neck round-bottomed flask along with phenylboronic acid (1.3 eq., 2.5361 g), tripotassium phosphate (3 eq., 10.1890 g), and bis(triphenylphosphine)palladium(II) dichloride (1 mol%, 112.3 mg). The reaction flask was flushed with N<sub>2</sub> for 15 minutes prior to solvent addition. After flushing with inert gas, 30 mL of degassed acetonitrile and 20 mL of



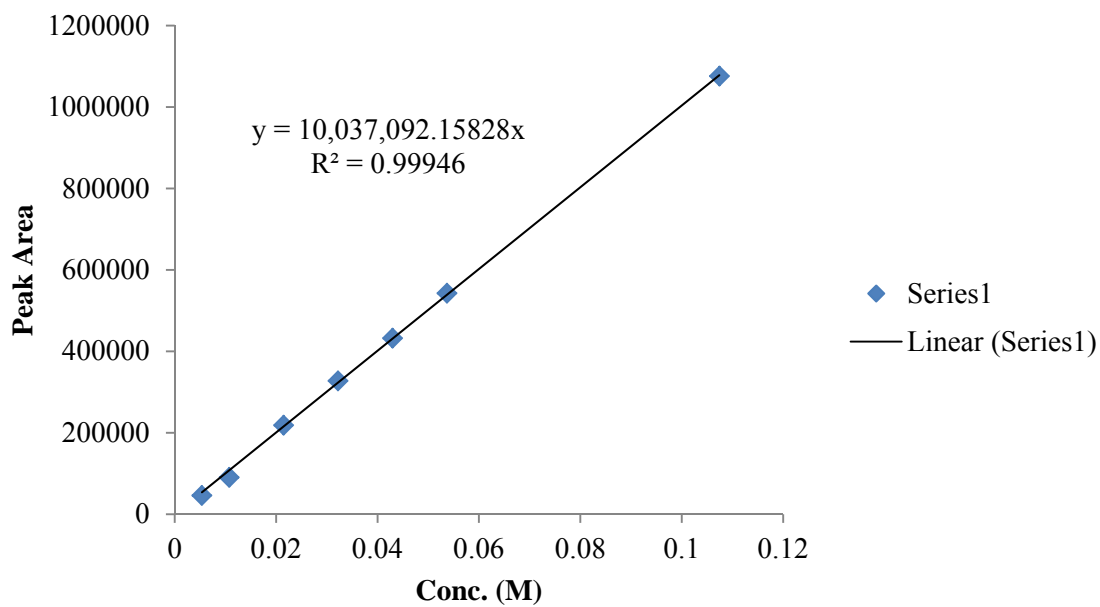
degassed H<sub>2</sub>O were added using air-tight syringes. The mixture was then heated to 70 °C and allowed to react for 5 hours with magnetic stirring (85% yield by GC).



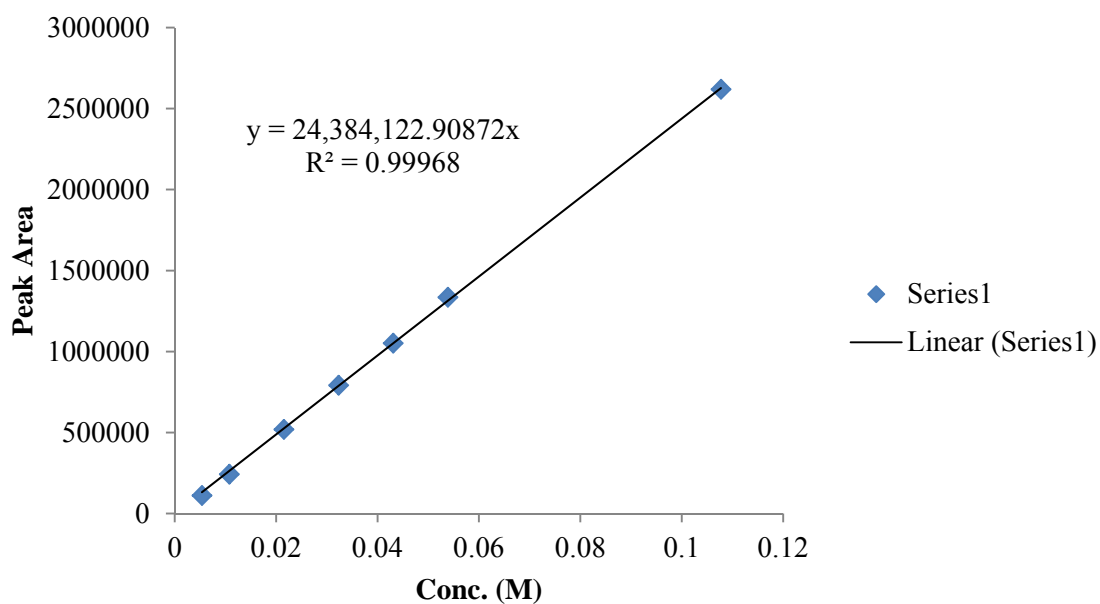
**Figure 4.2. GC-FID calibration of 5-methyl-2-phenylpyridine.**

#### 4.2.2.2 Suzuki Coupling of 2-bromopyridine

2-bromopyridine (16 mmol, 2.5280 g) was added to a 100 mL 3-neck round-bottomed flask along with phenylboronic acid (1.3 eq., 2.5361 g), tripotassium phosphate (3 eq., 10.1890 g), and bis(triphenylphosphine)palladium(II) dichloride (1 mol%, 112.3 mg). The reaction flask was flushed with N<sub>2</sub> for 15 minutes prior to solvent addition. After flushing with inert gas, 30 mL of degassed acetonitrile and 20 mL of degassed H<sub>2</sub>O were added using air-tight syringes. The mixture was then heated to 70 °C and allowed to react for 2 hours with magnetic stirring (80-90% yield by GC).



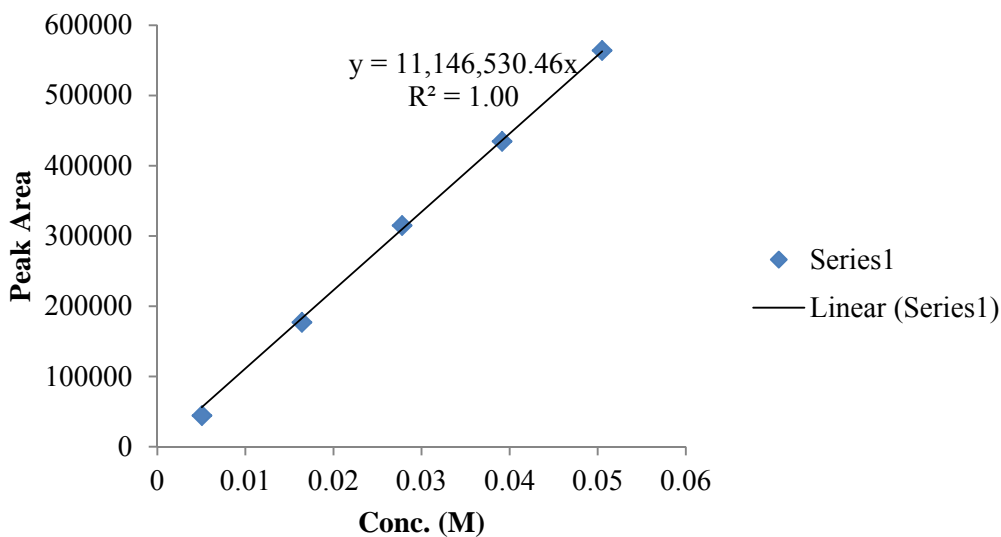
**Figure 4.3. GC-FID calibration curve 2-bromopyridine.**



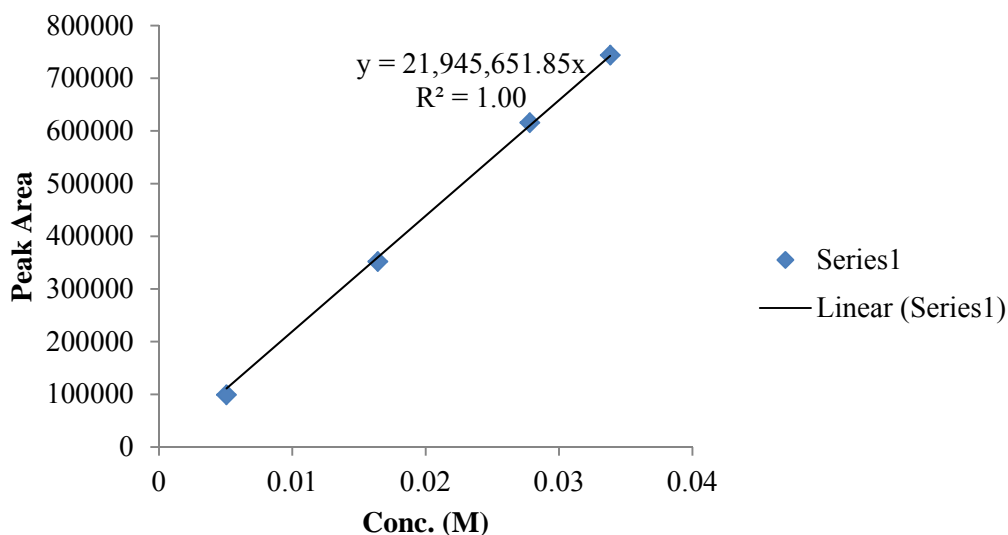
**Figure 4.4. GC-FID calibration curve. 2-phenylpyridine.**

#### 4.2.2.3 Suzuki Coupling of 4-Amino-2-bromopyridine

4-Amino-2-bromopyridine (16 mmol, 2.7682 g) was added to a 100 mL 3-neck round-bottomed flask along with phenylboronic acid (1.3 eq., 2.5361 g), dipotassium phosphate (3 eq., 8.3616 g), and bis(triphenylphosphine)palladium(II) dichloride (5 mol%, 0.5615 g). The reaction flask was flushed with N<sub>2</sub> for 15 minutes prior to solvent addition. After flushing with inert gas, 30 mL of degassed acetonitrile and 20 mL of degassed H<sub>2</sub>O were added using air-tight syringes. The mixture was then heated to 70 °C and allowed to react for 24 hours with magnetic stirring (90% yield by GC).



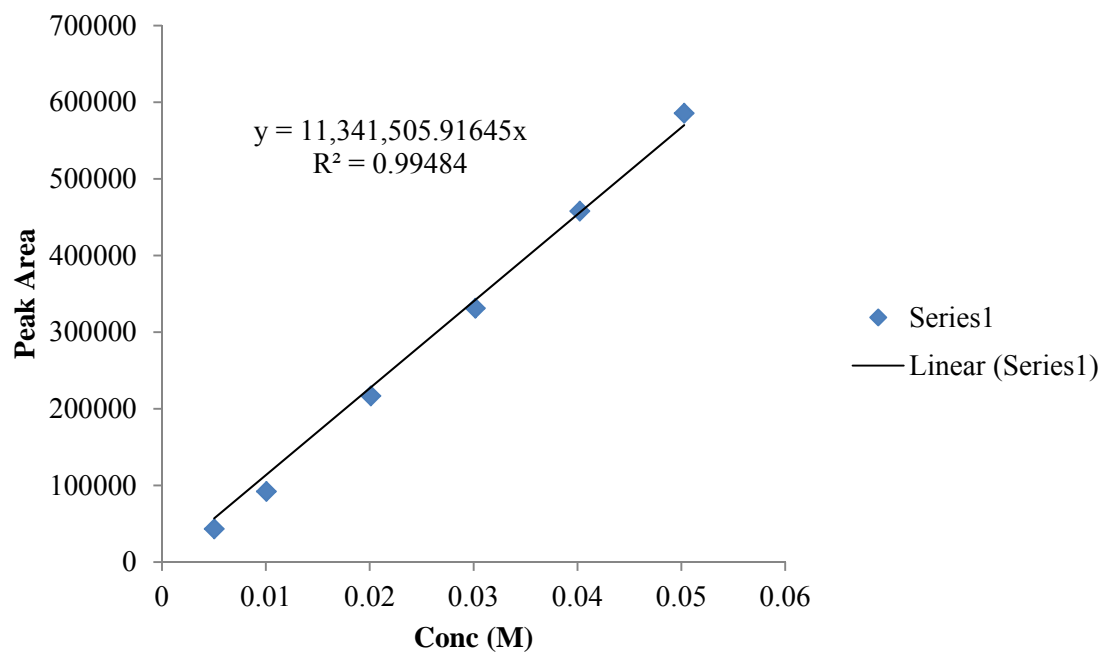
**Figure 4.5. GC-FID calibration curve for 4-amino-2-bromopyridine.**



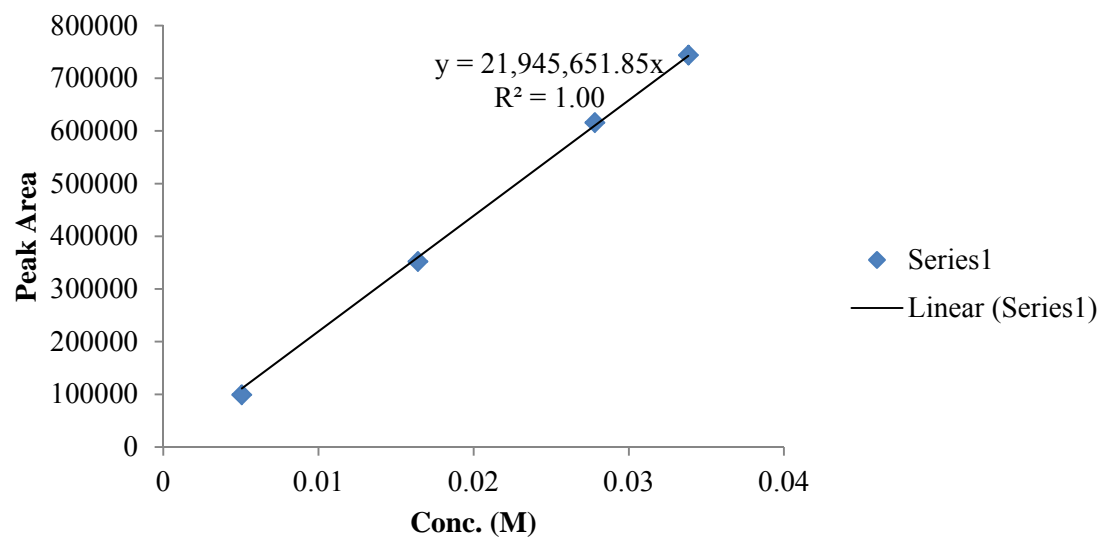
**Figure 4.6. GC-FID calibration curve for 4-amino-2-phenylpyridine.**

#### *4.2.2.4 Suzuki Coupling of 6-Amino-2-bromopyridine*

6-Amino-2-bromopyridine (16 mmol, 2.7682 g) was added to a 100 mL 3-neck round-bottomed flask along with phenylboronic acid (1.3 eq., 2.5361 g), tripotassium phosphate (3 eq., 10.189 g), and bis(triphenylphosphine)palladium(II) dichloride (1 mol%, 0.1123 g). The reaction flask was flushed with N<sub>2</sub> for 15 minutes prior to solvent addition. After flushing with inert gas, 30 mL of degassed acetonitrile and 20 mL of degassed H<sub>2</sub>O were added using air-tight syringes. The mixture was then heated to 70 °C and allowed to react for 4 hours with magnetic stirring (60% yield by GC).



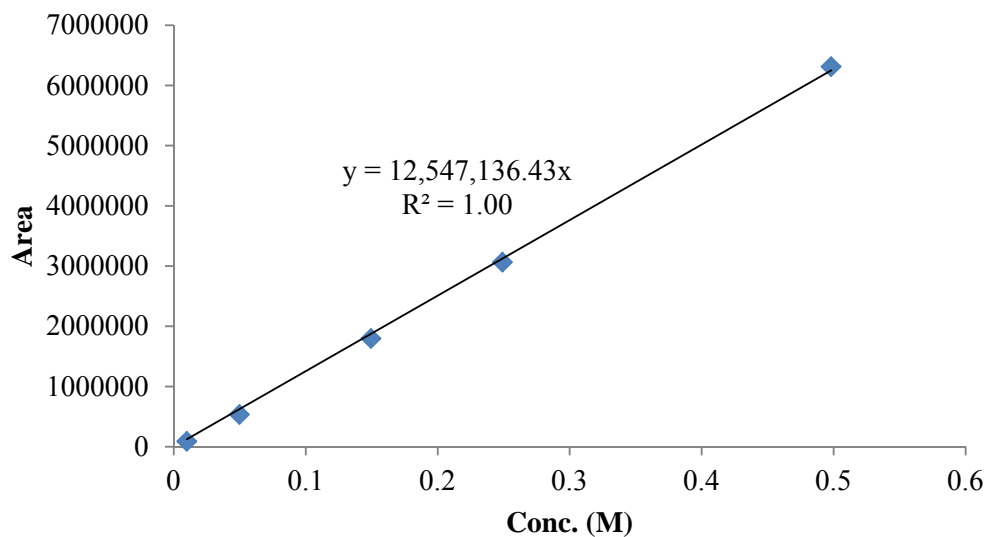
**Figure 4.7. GC-FID calibration curve of 6-amino-2-bromopyridine.**



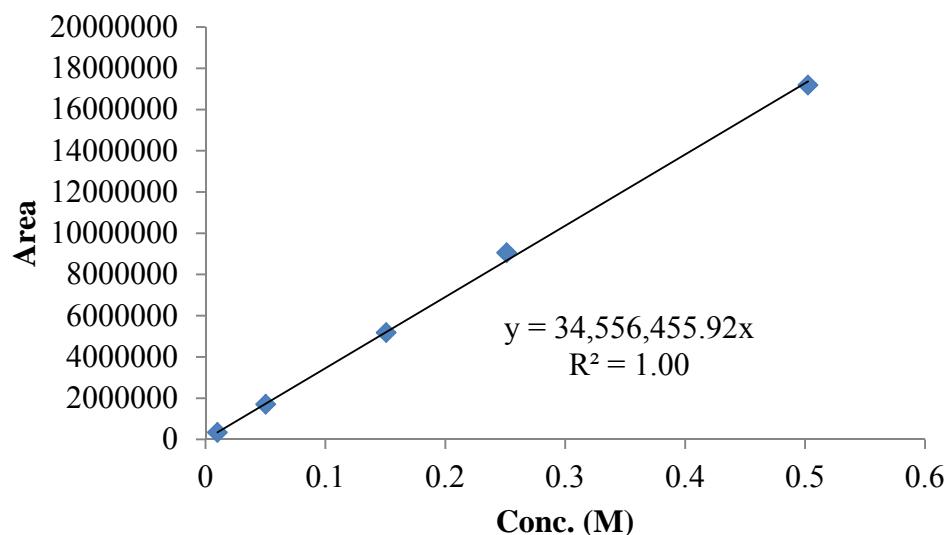
**Figure 4.8. GC-FID calibration curve of 6-amino-2-phenylpyridine.**

#### 4.2.2.5 Suzuki Coupling of 4-Bromoanisole

4-bromoanisole (16 mmol, 2.9926 g) was added to a 100 mL 3-neck round-bottomed flask along with phenylboronic acid (1.3 eq., 2.5361 g), tripotassium phosphate (3 eq., 10.189 g), and bis(triphenylphosphine)palladium(II) dichloride (1 mol%, 0.1123 g). The reaction flask was flushed with N<sub>2</sub> for 15 minutes prior to solvent addition. After flushing with inert gas, 30 mL of degassed acetonitrile and 20 mL of degassed H<sub>2</sub>O were added using air-tight syringes. The mixture was then heated to 70 °C and allowed to react for 20 minutes with magnetic stirring (>90% yield by GC).



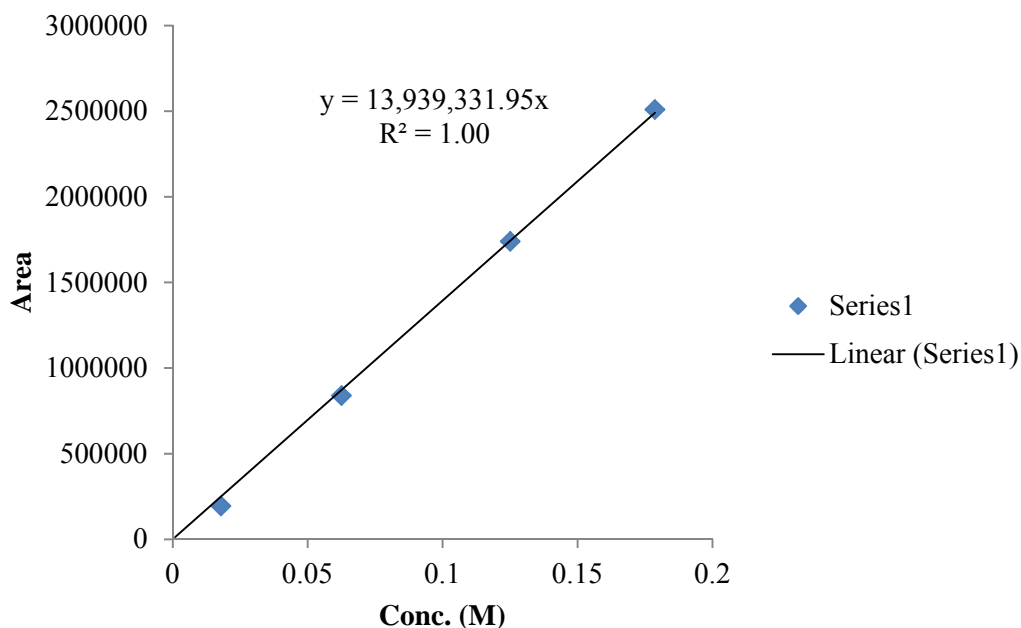
**Figure 4.9. GC-FID calibration curve. 4-bromoanisole.**



**Figure 4.10. GC-FID calibration curve. 4-methoxybiphenyl.**

#### 4.2.2.6 Suzuki Coupling of 2-bromo-5-cyanopyridine

2-bromo-5-cyanopyridine (16 mmol, 2.981 g) was added to a 100 mL 3-neck round-bottomed flask along with phenylboronic acid (1.3 eq., 2.5361 g), tripotassium phosphate (3 eq., 10.189 g), and bis(triphenylphosphine)palladium(II) dichloride (1 mol%, 0.1123 g). The reaction flask was flushed with N<sub>2</sub> for 15 minutes prior to solvent addition. After flushing with inert gas, 30 mL of degassed acetonitrile and 20 mL of degassed H<sub>2</sub>O were added using air-tight syringes. The mixture was then heated to 70 °C and allowed to react for 15 minutes with magnetic stirring (>90% yield by GC).



**Figure 4.11. GC-FID calibration curve. 2-bromo-5-cyanopyridine.**

#### 4.2.2.7 CO<sub>2</sub>-Induced Separation: Function of Pressure Studies

Follows the procedure in 3.2.2.5

#### 4.2.2.8 CO<sub>2</sub>-Induced Separation: Total Decant Studies. No additional solvent

Separations under CO<sub>2</sub> incorporating “no additional solvent” follow the procedure in 3.2.2.7, with a key difference. Following removal of the post-reaction aqueous phase, 20mL H<sub>2</sub>O and additive is added to the remaining organic phase. The mixture is then transferred to the Parr vessel (3.2.2.2) and separation proceeds.

#### 4.2.2.9 CO<sub>2</sub>-Induced Separation: Total Decant Studies. No additional solvent. Wash step

Separations are performed following the procedure in 4.2.2.8; however, 20mL H<sub>2</sub>O is added without additive. This aqueous phase is removed and 20mL of fresh H<sub>2</sub>O is



added with additive. The mixture is then transferred to the Parr pressure vessel (3.2.2.2) and separation experiments are performed.

#### *4.2.2.10 Toluene Separation: Wash step*

Follows procedure in 4.2.2.9; however, the 20mL H<sub>2</sub>O is added for the first time, 5mL toluene is added as well. The aqueous phase is removed and 20mL fresh H<sub>2</sub>O and additive are added to the system. Using syringes, samples are then taken from each phase, the pH is measure using a digital pH meter, and the volumes of each phase are measured using a 100mL airtight syringe. Product and Pd amounts are then analyzed using GC-FID and atomic absorption.

#### *4.2.2.11 Recycle Reactions*

Recycle reactions are performed using the aqueous phase following one of the separations outlined previously. In a 3-neck, 100mL flask, 16mmol reaction substrate, 1.3 eq. phenylboronic acid, 4.7 eq. base (adjusts pH to ~13 due to acidity of additive used), and a specified amount of triphenylphosphine ligand are purged under N<sub>2</sub> for 15-30minutes. 30mL degassed ACN and the separated aqueous phase are added to the purged mixture. The mixture is then heated to 70 C with magnetic stirring and the reaction proceeds under N<sub>2</sub>. Turnover frequency (TOF) is used to compare catalytic activity for these reactions. TOF is defined below.

$$TOF = \frac{mmol\ Pr\ oduct}{mmolPd * Time(h)}$$

**Equation 4.1**

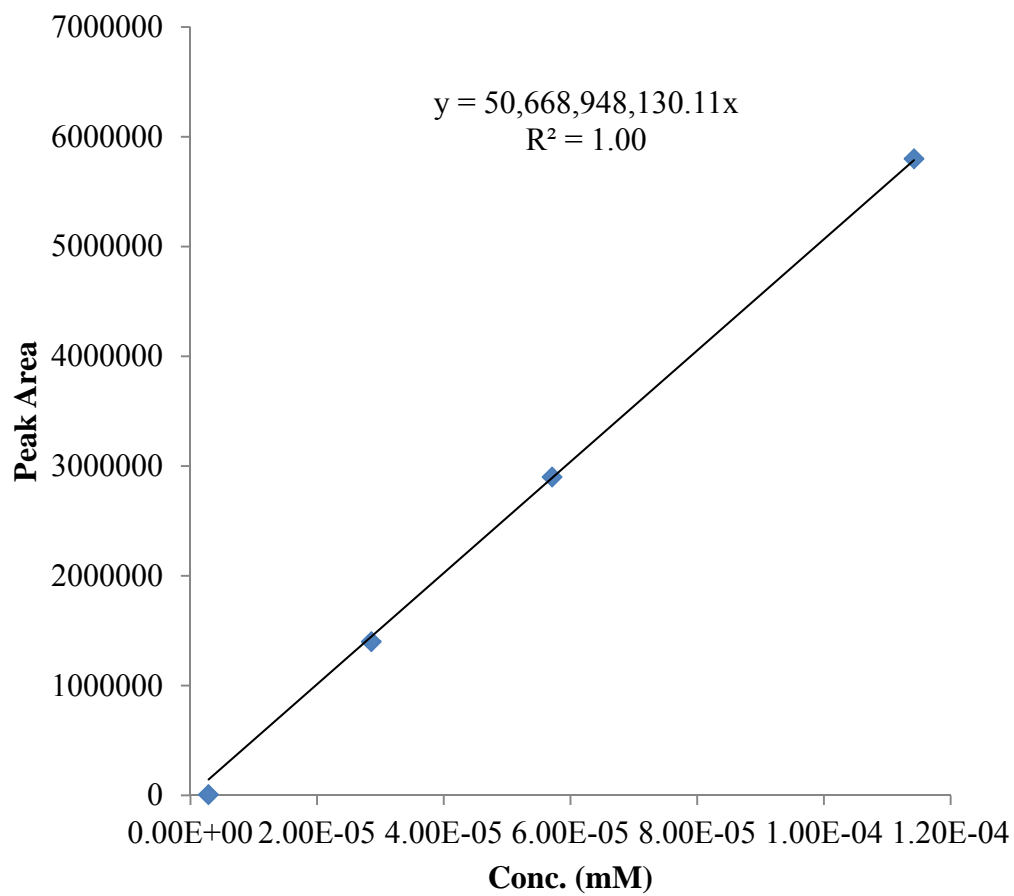
#### 4.2.2.12 Control Separations

In a 6-dram vial, based on a 4.3 mmol basis, 1mol% catalyst (Pd-dba or tetrakis), the specified amount of 5-methyl-2-phenylpyridine and 5-methyl-2-bromopyridine (100%,80%,or20%) are added with a magnetic stirrer. The cap of the vial is removed and sealed with a septa. The vial is then purged with N<sub>2</sub> for 10 minutes. 8mL ACN, 5.3mL H<sub>2</sub>O, and 1.3mL Toluene are added to the vial. HCl is then used to adjust the pH as need. Samples and phase volumes are measure via airtight syringe.

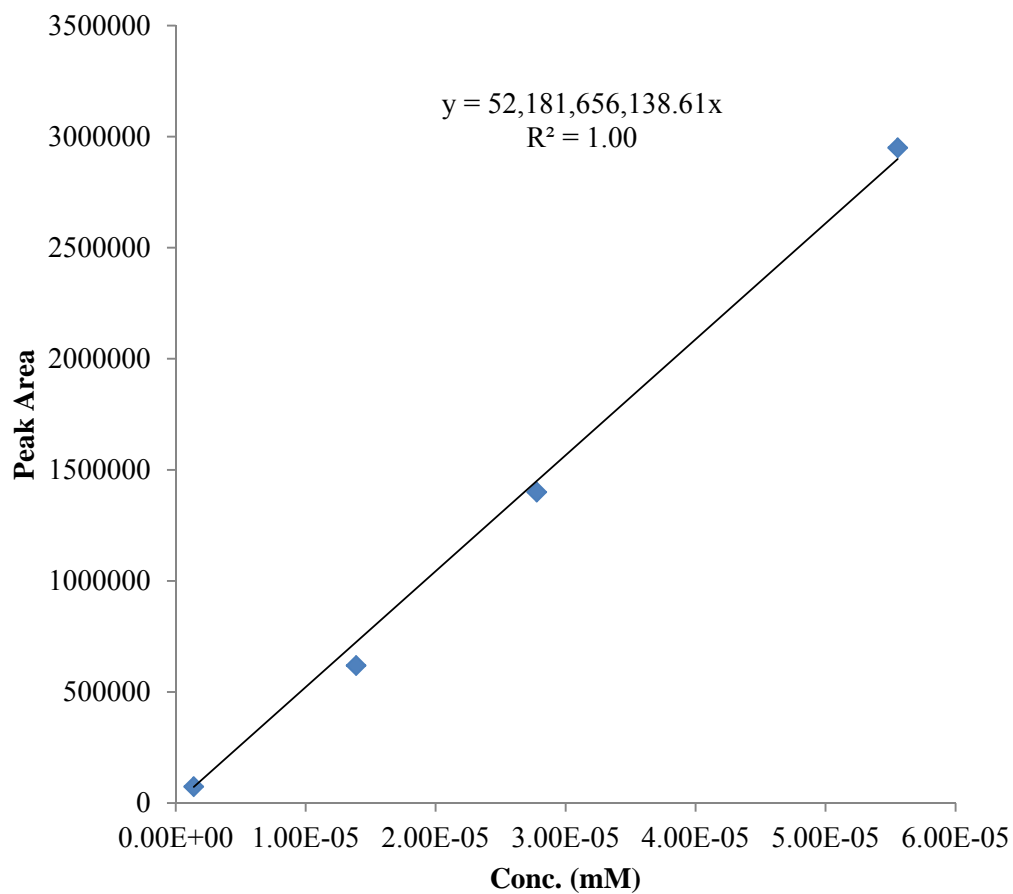
#### 4.2.3 Instrumentation

Palladium concentration was measured using a Shimadzu AA-7000F Atomic Absorption Spectrometer, measuring as 244.7 nm. Background noise was removed from signal by self-reversal, with a current swing of 10 mA – 300 mA. Analysis occurred at a fuel gas flow rate of 1.8 l/min and an air flow rate of 15 l/min. Calibration curves were prepared by dissolving known amounts of bis(benzonitrile)palladium(II) dichloride into a 0.4% solution of (poly)ethyleneimine in 60/40 MeCN/H<sub>2</sub>O. Samples for analysis were dissolved in a 0.4% solution of (poly)ethyleneimine in 60/40 MeCN/H<sub>2</sub>O.

Concentrations of reaction substrates, products, triphenylphosphine and triphenylphosphine oxide were measured using a Shimadzu GC-FID with calibration curves dissolved in 60/40 MeCN/H<sub>2</sub>O. Samples were diluted in ACN to concentrations which fell within calibration curves. The GC-FID methods used an initial and final oven temperature of 195 °C and 320 °C and a gradient of 15 °C/min (5-cyano-2-brompyridine reaction product and substrate used an initial oven temperature of 150 °C). Calibration curves of reaction products and reactants are shown previously in the experimental section while calibration curves for TPP and TPP-oxide are shown below.



**Figure 4.12. GC-FID Calibration Curve. TPP**



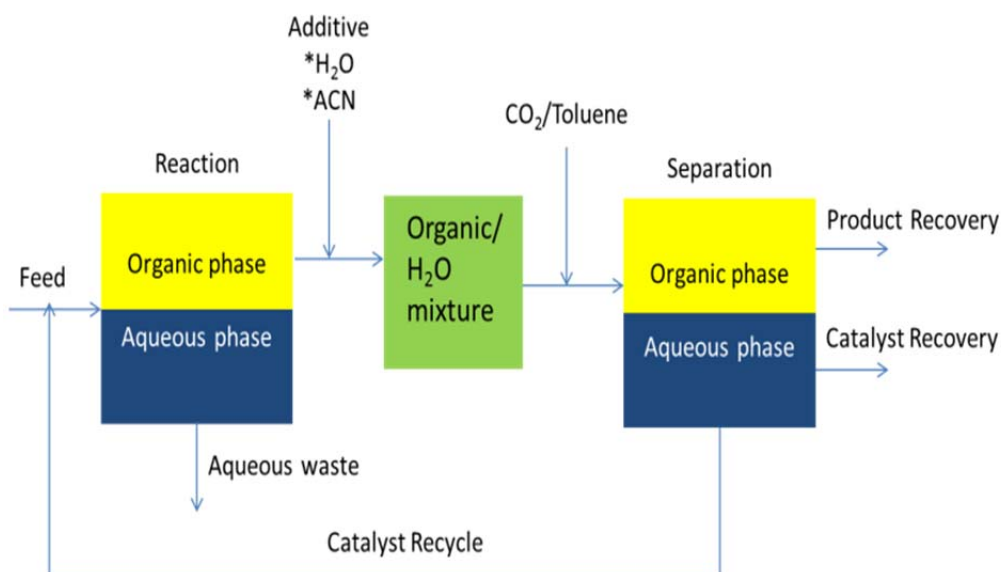
**Figure 4.13. GC-FID Calibration Curve. TPP-O.**

$^{31}\text{P}$ -NMR experiments were performed on a Bruker AMX-400 NMR machine using 256 scans. Samples were prepared by adding 0.2mL of sample to 0.3mL of MeOD (D-4) in a NMR tube. A capillary tube containing an 85% solution of phosphoric acid was used as a reference peak and set to ppm = 0.

## 4.3 Results and Discussion

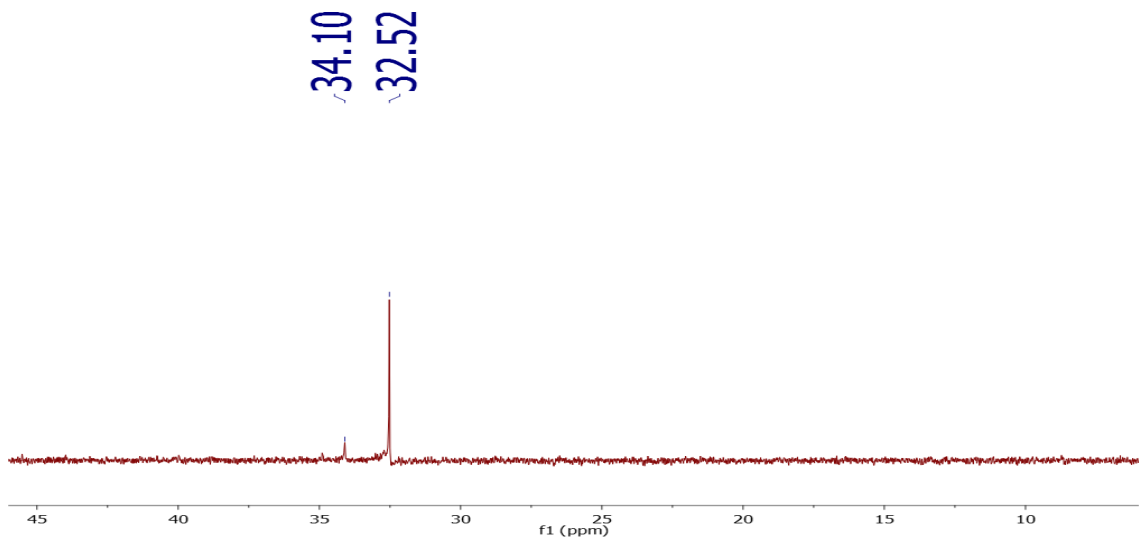
### 4.3.1 5-Methyl-2-phenylpyridine. Process Optimization

#### 4.3.1.1 No wash step. Solvent reduction and additive selection.



**Figure 4.14. Process Scheme.** \*Following reaction, experiments performed a). 28 mL ACN and 42 mL H<sub>2</sub>O are added b). 20 mL H<sub>2</sub>O added.

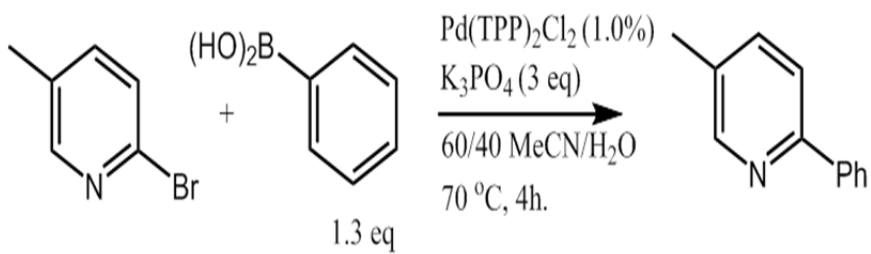
The reaction of 5-methyl-2-bromopyridine achieves 80-90% yields in 4 hours at 70 °C using acetonitrile (ACN) and water as solvents with a potassium phosphate base. Following reaction, both catalyst and product are soluble and remain in the organic phase, while the majority of inorganic base remains in the post reaction aqueous phase.



**Figure 4.15.** Post-reaction  $^{31}\text{P}$ -NMR of Scheme 4.1.

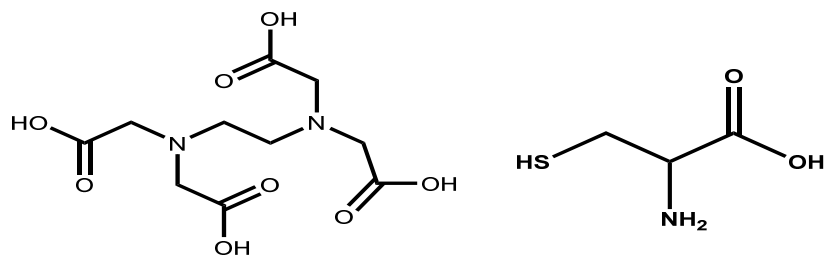
Additionally, the post-reaction P-NMR (Figure 4.15) indicates the presence of oxidized TPP species (34 and 32.5 ppm) and no Pd-bound phosphine.

The initial separation studies following the scheme in Figure 4.14.



**Scheme 4.1.** Suzuki coupling reaction of 5-methyl-2-phenylpyridine.

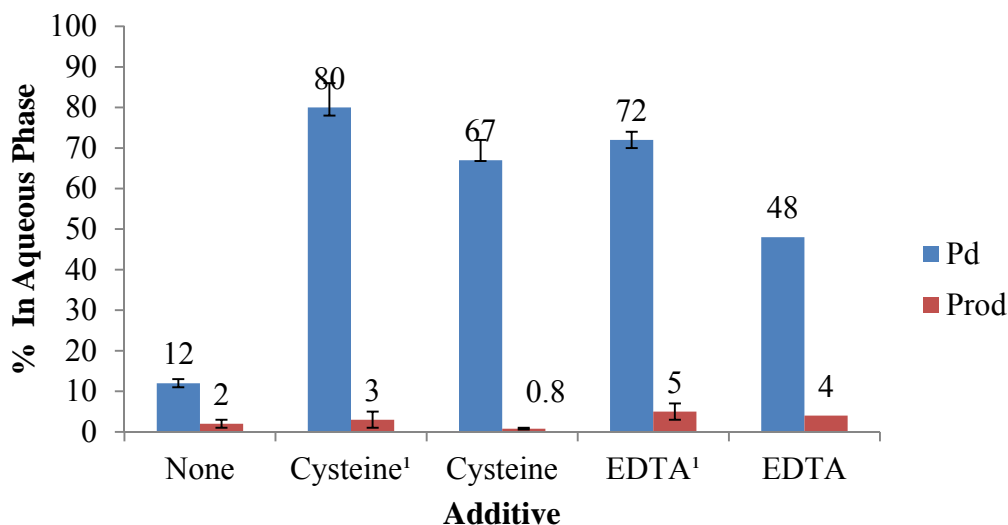
As Figure 4.14 decantation of this post-reaction aqueous phase allows for facile removal of any inorganics in the system. H<sub>2</sub>O and ACN, both added in excess in order to measure phase volumes in the windowed Parr (4.2.2.7), are then added to the remaining organic phase, creating a one-phase mixture. The addition of CO<sub>2</sub> or toluene as an anti-solvent then induces a phase split. Early baseline results (no additive, Figure 4.17) show 12% of palladium and 2% of product in the aqueous phase, thus additive selection was determined as a key parameter for separation. The previous chapter (CHAPTER 3 -) details a thorough additive screening. EDTA (acidic) and cysteine (Figure 3.15) are both inexpensive additives which are known to chelate with palladium<sup>8,19</sup>. Separations using these compounds give 72% and 80% palladium in the aqueous phase (using 20eq. of additive) at 400psi CO<sub>2</sub> pressure with less than 5% product in the aqueous phase. Due to their success in separating palladium, both cysteine and EDTA were chosen for further study in this work.



**Figure 4.16. EDTA and Cysteine.**

While the separations described in the previous paragraph give good results, the addition of excess solvent prior to separation represents a limitation. From a vessel and reactor design perspective, it is undesirable to add excess solvent to the system, thus separation experiments were performed following the process in Figure 4.14, but only

20mL of H<sub>2</sub>O (the volume added to fresh Suzuki reactions) is added following removal of the post-reaction aqueous phase. Figure 4.17 shows these separations results. When less solvent is added, there is a significant decrease in aqueous Pd amount, 80% to 67% for cysteine and 72% to 42% for EDTA. This presents a challenge in the separation.



**Figure 4.17. Separation data under 400psi CO<sub>2</sub> pressure with 20 eq. (of Pd) of additive . Pd = palladium, prod = 5-methyl-2-phenylpyridine. <sup>1</sup>Excess ACN and H<sub>2</sub>O added to system prior to separation. 20 eq. of additives used.**

Work in Chapter 3 indicates that the acidity of additives plays a role on the partitioning of the product (Figure 3.14). To evaluate whether this acidity may also effect the Pd partitioning, separations were performed under CO<sub>2</sub> pressure following Figure 4.14, but with only 20mL H<sub>2</sub>O added following decantation of the aqueous phase and 5mL toluene added in lieu of CO<sub>2</sub> pressure. Two separate experiments with different

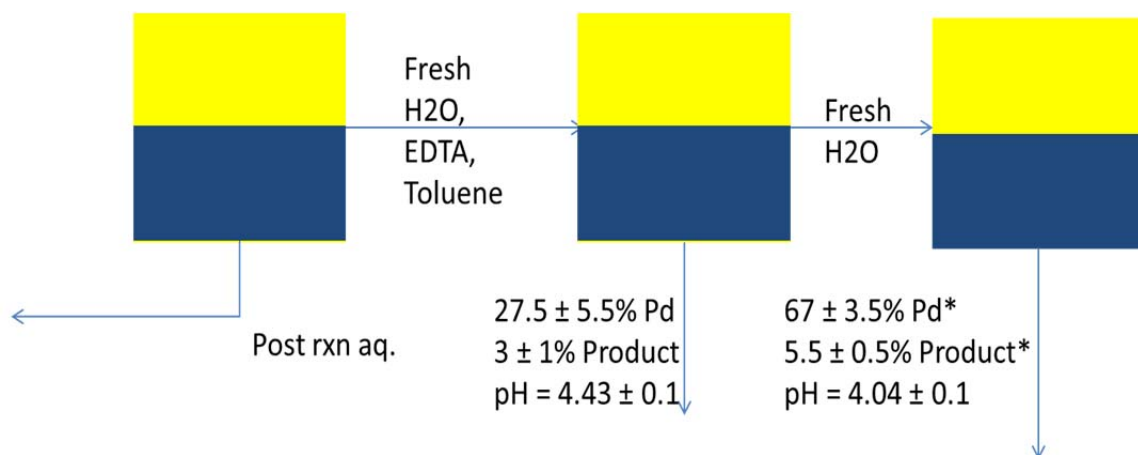


additives were performed: 20eq. EDTA and HCl added until the system reached a corresponding pH. The results are shown in Table 4.1.

**Table 4.1. Separations with toluene. Follows Figure 4.14 but only 20mL H<sub>2</sub>O added following decantation and 5mL Toluene added instead of CO<sub>2</sub> pressure.**

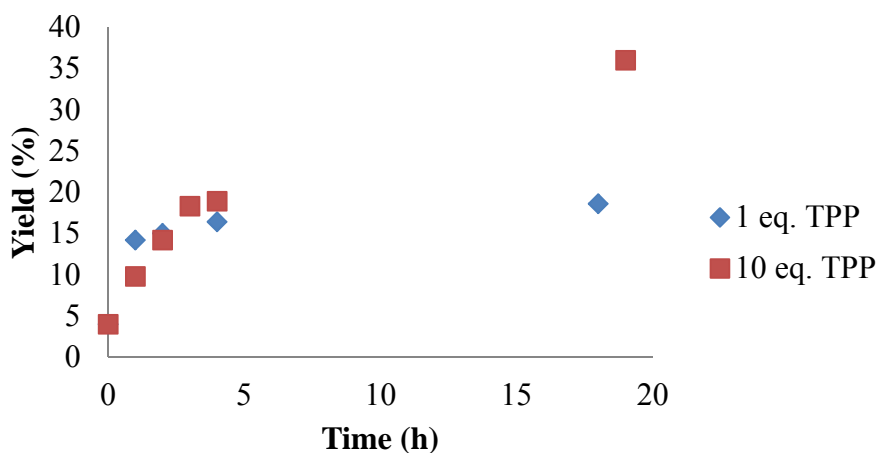
Additive	pH	% Pd aq.	% Product aq.
HCl	4.39	30	3
EDTA(20eq)	4.43 ± 0.1	28 ± 6	3 ± 1

Table 4.1 shows, when EDTA and HCl are added and the pH is ~4.4, 28% and 30 % of Pd and 3% of product are found in the aqueous phase. These are comparable separations and indicate that EDTA's primary effect may simply be adjusting the pH. Additionally, the amount of aqueous Pd is lower compared to CO<sub>2</sub> separations under similar conditions (Figure 4.17).



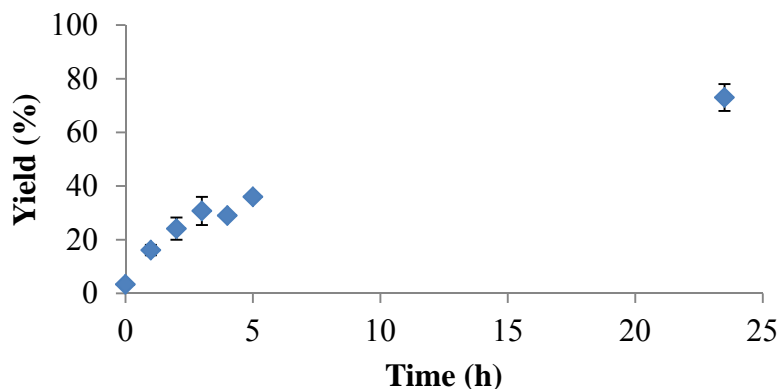
**Figure 4.18. Process of Multi-stage extraction using 5mL toluene. \*% of total amount left following 1<sup>st</sup> separation. 20mL H<sub>2</sub>O added at each separation stage.**

As a means of improving the separation of Pd from reaction product, a multi-stage extraction was performed using toluene as the anti-solvent (Figure 4.18). 20mL H<sub>2</sub>O was added in each extraction stage. In the first stage, 28% of Pd and 3% of product is present in the aqueous phase. However, the second separation gives 67% of remaining Pd in aqueous phase following 1<sup>st</sup> extraction.



**Figure 4.19. Recycle of Pd separated in Table 4.1/first separation. 4 hour Turnover frequency: 1 eq. TPP: 14, 10 eq. TPP: 23.**

The Pd-containing aqueous phase separated in Table 4.1 is added to fresh reactants, acetonitrile, base, and different amounts of TPP ligand to perform recycle reactions. Results of recycle are shown in Figure 4.19. Recycle reactions with 1eq. and 10eq. of TPP show reactivity with turnover frequency (TOF) of 14 (1eq TPP) and 23 (10eq TPP).

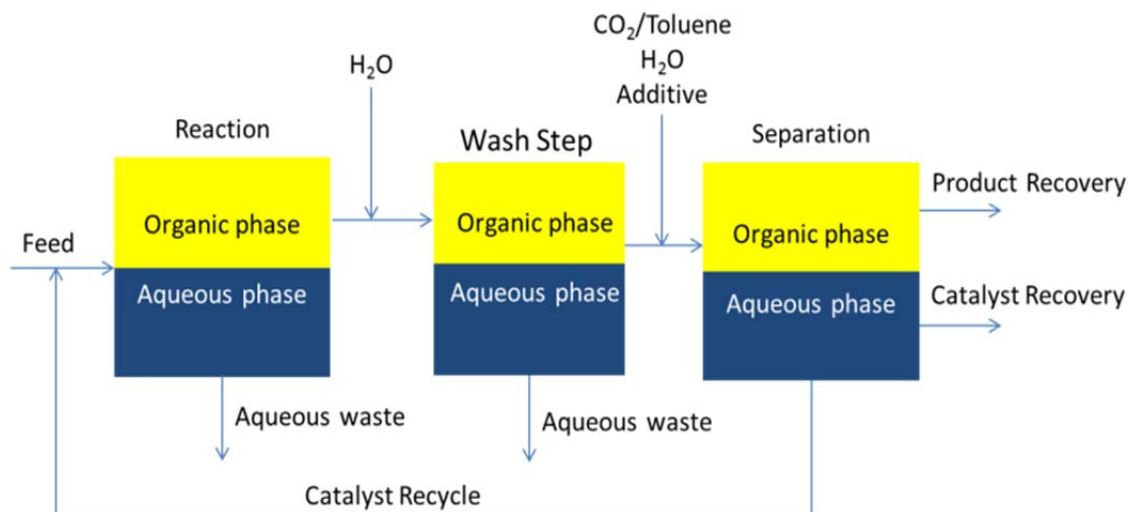


**Figure 4.20. Recycle of Pd separated in 2<sup>nd</sup> extraction in Figure 4.18.**

The Pd separated in the second extraction in Figure 4.18 is recycled with 10 eq. TPP. The reaction gives a TOF of 31 at 3h. Thus, the Pd separated following separation with EDTA still shows reactivity.

In addition to separated Pd to perform chemistry, all of the palladium remained in the organic phase. Thus, EDTA was chosen as an optimum sacrificial additive for this process, and experiments were performed to optimize both separation and recycle in this process.

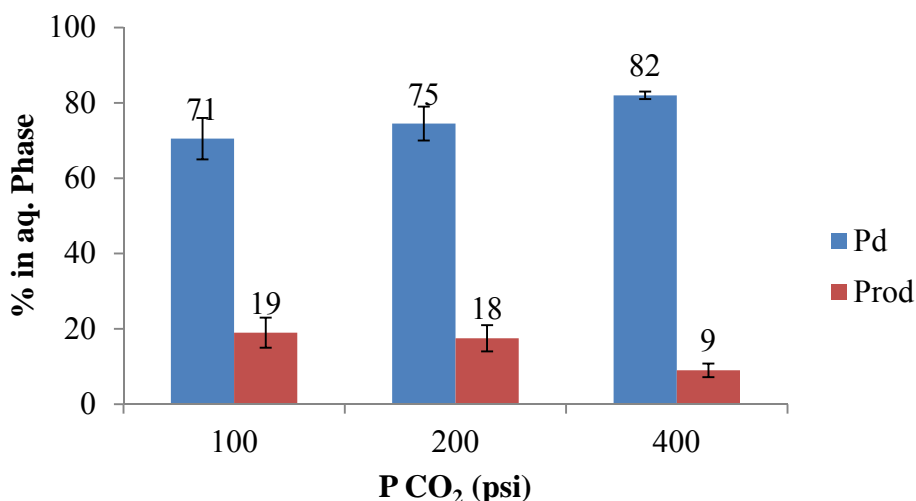
#### 4.3.1.2 Addition of “wash step”



**Figure 4.21. Separation scheme with wash step.**

Based on the result in Figure 4.18, a key modification in the separation process was made through the addition of a “wash step”. The revised process is shown in Figure 4.21. When 20mL of H<sub>2</sub>O are added following removal of the post-reaction aqueous phase, a phase split occurs; however, negligible amounts of Pd and ~10% of reaction product are found in the aqueous phase. This aqueous phase is removed and fresh water, additive and anti-solvent are added to the remaining organic phase to perform separation. Figure 4.22 shows the results of this EDTA separation as a function of CO<sub>2</sub> pressure. At 400psi CO<sub>2</sub>, 82% of Pd and 9% of reaction product is found in the aqueous phase. Compared to the result in Figure 4.17 (48% and 4% aqueous Pd and product at 400psi) which did not incorporate a “wash step,” this is a significant improvement in separation and demonstrates the value of adding a wash step. Additionally, <sup>31</sup>P-NMR shows no

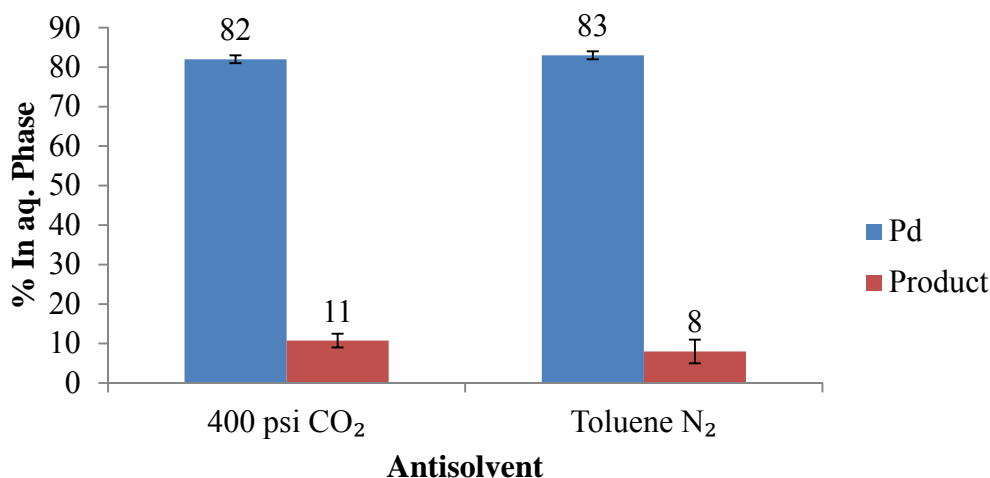
traces of phosphate salt in the aqueous phase of the separation following the wash step (phosphate salt is seen in prior separations). The difference in phosphate salt amount is an indication that the wash step could help this system by removing inorganic salts.<sup>20-21</sup>



**Figure 4.22. Wash-step separation. Function of CO<sub>2</sub> pressure.**

Since pressure is a key parameter in vessel design cost, it is more desirable to obtain good separation at lower CO<sub>2</sub> pressures. Figure 4.22 shows the amount of Pd in the aqueous phase is relatively constant (71-82% from 100 to 400psi) as CO<sub>2</sub> pressure changes; however, CO<sub>2</sub> pressure does appear to have an effect on the partitioning of product. As the CO<sub>2</sub> pressure increases from 100 to 400 psi, the amount of product in the aqueous phase decreases from 19% to 9%. This result is important, for there is less product recovery in the organic phase, an undesirable outcome with higher-value products. Additionally, a higher amount of coordinating product in the aqueous phase could hinder palladium recycle.

Based on the separation results as a function of CO<sub>2</sub> pressure and the results in Table 4.1, the role of CO<sub>2</sub> in this system must be considered. Previous work shows that as CO<sub>2</sub> pressure is increased in an ACN/H<sub>2</sub>O system, the fraction of water in the ACN-rich phase decreases and the kamlett-taft parameter of the ACN-rich phase decreases as well, making the phase less polar and increasing the solubility of the product in this phase.<sup>22-23</sup> This information, combined with the results in Figure 4.22, indicate that the primary role of the CO<sub>2</sub> in this system is to simply improve the phase split in this system.<sup>22</sup> As a means of evaluating this theory, a separation was run with EDTA as an additive following the scheme in Figure 4.21, but using toluene as an anti-solvent.

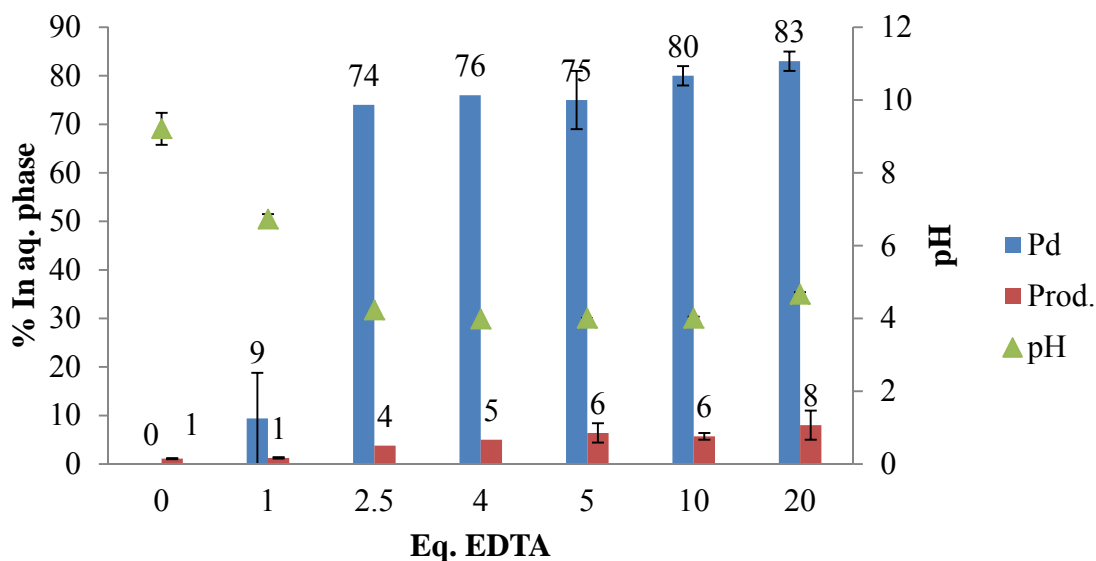


**Figure 4.23. CO<sub>2</sub> toluene separation comparison. Wash step.**

Figure 4.23 shows a comparison between using CO<sub>2</sub> and toluene as anti-solvents. In both cases, the Pd and product results are identical within experimental error, giving 82% and 83% Pd and 11% and 8% product in the aqueous phase, respectively. The

comparable performance indicates that the primary role of CO<sub>2</sub> is to improve the phase split between the organic and aqueous phases within this system, thus improving product partitioning into the organic phase.

Given the comparable performance between anti-solvents, further separation experiments were performed using toluene to examine the effect of EDTA loading on separations.

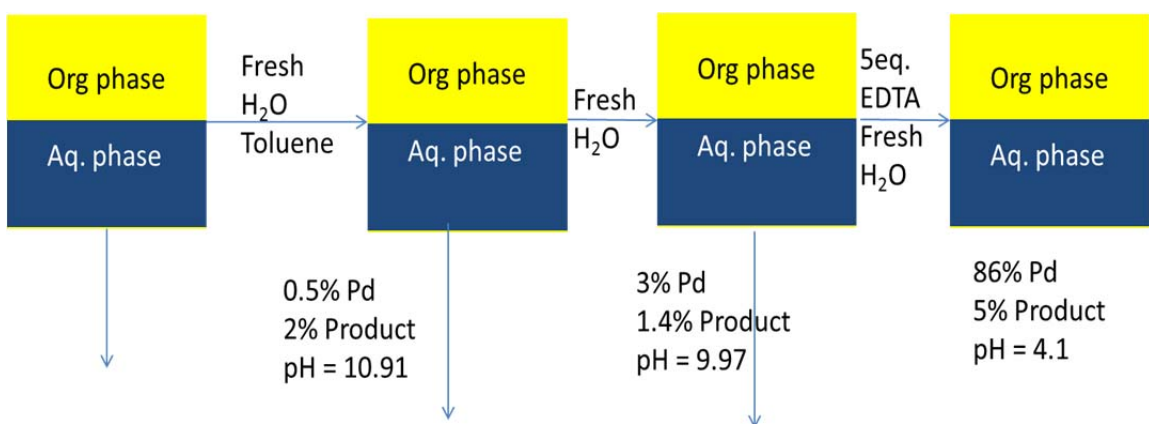


**Figure 4.24. Separation as a function of EDTA eq. Toluene used as anti-solvent.**

Figure 4.24 shows the effect of EDTA loading on separation. The results show that 0, 1, 2.5, 4, 5, 10, and 20 eq. of EDTA (relative to palladium) give 0%, 15%, 74%, 76%, 75%, 80%, and 83% Pd and 1%, 1%, 4%, 5%, 6%, 6%, and 8% product in the aqueous phase. This indicates that, while more than 1 equivalent of EDTA is necessary

for separation, there isn't significant improvement at EDTA equivalences higher than 2.5. Thus, it appears that 2.5 eq. of EDTA is the optimum additive loading.

Having established toluene as an effective anti-solvent, the effectiveness of using a “wash step,” and the effect EDTA loading on separation, the role of a second wash step was probed.



**Figure 4.25. Separation experiments using 5eq. EDTA, Toluene during the washing step, and multiple washes. 20mL H<sub>2</sub>O is added at each stage.**

Figure 4.25 shows a separation using 2 wash steps and 5eq. EDTA. Toluene is added prior to the wash steps and appears to reduce product losses during the wash step. The separation at pH = 4.1 gives 86% of Pd and 5% product in the aqueous phase. The amount of aqueous Pd is only slightly higher than separations with only 1 wash (75% aqueous Pd). However, when considering a metal as expensive as Pd, this extra wash step may be worthwhile.

Over the course of the Suzuki coupling reaction from which produces the product from which Pd is separated (Scheme 4.1 ), 50-70% of the phosphine ligand is oxidized



and no Pd-bound phosphine is seen by NMR analysis (Figure 4.15). Thus, the effect that the presence of TPP may have on the separation was examined.

**Table 4.2. Addition of TPP to separation system. Separation performed with 5eq. EDTA.**

Step.	Eq. (of Pd) TPP Added	pH	% Pd Aq.	% Prod. Aq.
1	No addition	4.04	78	5
2	5	4.07	49	5
3	10	4.17	46	5

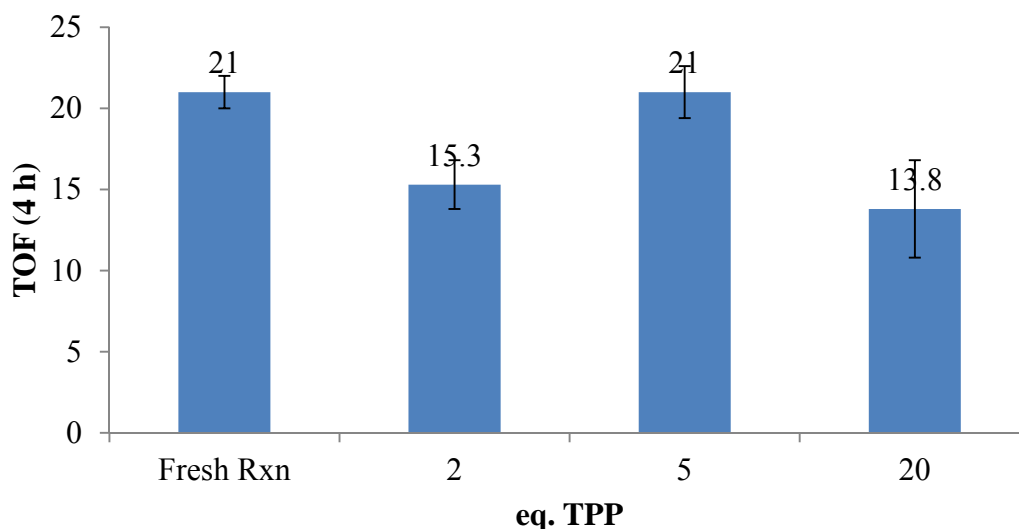
Table 4.2 shows that when 5 and 10 eq. of TPP are added to the separation system the amount of Pd in the aqueous phase is reduced from 78% to 49% and 48%, respectively. The amount of aqueous product is unchanged at 5%. Thus, it appears that the presence of TPP is detrimental to this separation and the oxidation of this ligand during reaction is beneficial to separation.

#### *4.3.1.3 Catalyst Recycle and Separation Following Recycle*

With conditions established for an optimum separation (wash step(s), toluene anti-solvent, 2.5-5eq. EDTA), subsequent experiments in which the separated palladium is recycled were then carried out. Recycle experiments follow the process in Figure 4.21 using 5eq. EDTA in the separation stage. The aqueous phase of the separation is added to

fresh acetonitrile, starting material, phenylboronic acid, base (adjusted to optimum reaction pH), and triphenylphosphine.

Since very little (<10%) of triphenylphosphine is present in the aqueous phase during separation and “fresh” Suzuki reactions are run with pre-complexed Pd-TPP catalyst, the amount of fresh TPP added prior to recycle reaction was determined as a key parameter for examination in recycle experiments.



**Figure 4.26. Recycle reaction summary. TOF = Turnover frequency (mmol Prod/mmol Pd/hours). Prod = 5-methyl-2-phenylpyridine. TPP = triphenylphosphine.**

Figure 4.26 shows the turnover frequencies (TOF) of both the fresh Suzuki coupling reaction and recycle reactions run with varying amounts of triphenylphosphine (TPP) added following separation. The data clearly demonstrates that the amount of TPP added for recycle reactions has a large effect on the activity of the recycled catalyst. 5

equivalents of TPP added following separation give a turnover frequency (21) comparable to that of the fresh reaction (21) using a pre-complexed Pd-TPP catalyst. Interestingly, recycle reactions run with 2 eq. of TPP give a lower TOF (15.3) than fresh reactions with 2eq. of TPP pre-complexed to Pd. Behavior of TPP in the reaction system explains this difference. A significant amount of TPP (1-2 eq. relative to Pd) is oxidized during recycle reactions, likely by hydroxide present in the basic reaction conditions used<sup>24</sup>. Thus, an excess (> 2eq.) of TPP is needed to gain comparable reactivity in recycle reactions.

Figure 4.26 also shows that too much TPP hinders catalytic activity (recycles run with 20 eq. TPP gives a TOF of 13.8). It is likely that the large amount of TPP competes with substrate for access to the palladium catalyst, thus slowing reaction

Following completion of the recycle reaction, subsequent separation of Pd from reaction product was examined. When considering separations following recycle reactions, a few post-reaction parameters must be considered. First, all of the recycled Pd is both soluble and present in the organic phase of the reaction. Second, LCMS analysis indicates the presence of EDTA in the aqueous phase, but not in the organic phase. Thus, when the post-reaction aqueous phase is removed (Figure 4.21) no catalyst is lost, but fresh EDTA must be added for separations. Finally, with excess TPP added prior to recycle reaction, separation may become more difficult (Table 4.2).

**Table 4.3. Post-Recycle Separations. Prod: 5-methyl-2-phenylpyridine.**

Eq. TPP Prior to Recycle	Recycle Time (h)	eq. TPP Remaining	Wash Step	Separation Conditions	% Pd aq.	% Prod aq.	pH
2	21	0	yes	10 eq. EDTA, 400psi CO <sub>2</sub>	45	7	
2	18	0	yes	20 eq. EDTA, Toluene	60	6	4.88
5	4	2.25	2 washes	5 eq. EDTA, toluene	64	4.5	4.5
5	6	1.5	2 washes	5 eq. EDTA, toluene	65	5	4.19

Table 4.3 shows the results of experiments in which Pd is separated from reaction product following recycle reaction. Given that additive loading, presence of TPP, anti-solvent, and number of washes all can effect separation of Pd from reaction product, all of these conditions are also listed in Table 4.3.

Recycle reactions with 2eq. of TPP added are run for 18 and 21 hours. Following the reaction all TPP is oxidized. Separations using 10eq. EDTA and 400psi CO<sub>2</sub> give 45% Pd and 7% product in the aqueous phase. Separation using 20eq. EDTA and Toluene gives 60% Pd and 6% product in the aqueous phase (pH = 4.88). Both values are slightly lower than the ~75% aq. Pd seen in separations following a fresh Suzuki reaction.

Recycle reactions with 5eq. TPP added before reaction are run for 4 and 6 hours resulting in 2.25 and 1.5 eq. of TPP remaining. 2 wash steps are performed and separation is performed with 5eq. EDTA and toluene. These separations result with 64% and 65% Pd and 4.5% and 5% product in the aqueous phase at pHs of 4.5 and 4.19. These separations are slightly lower than separations performed on original reactions under

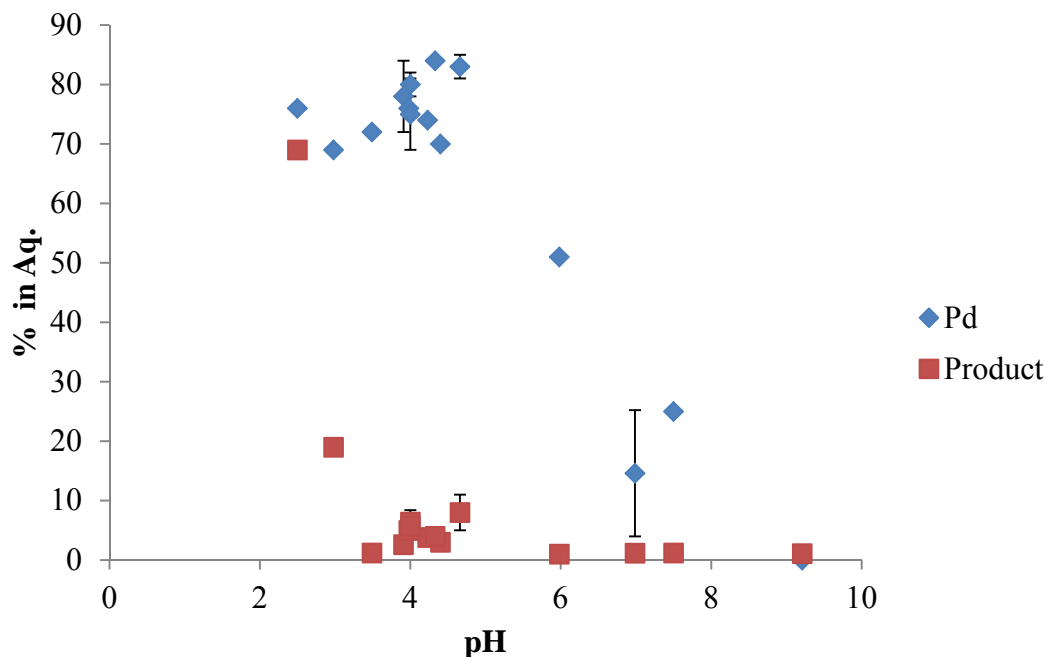
comparable conditions (Figure 4.24, Figure 4.25). This is possibly due to the higher amount of phosphine present following recycle reaction. The Pd from one of these separations was recycled once again using 5eq. of TPP and reaches a TOF of 28.

The work thus far has demonstrated that successful separation and recycle of palladium from 5-methyl-2-phenylpyridine following Suzuki coupling reaction can be achieved using inexpensive solvents, ligands, and acidic EDTA as an additive. In an effort to both understand this separation technique further and establish its versatility, the pH of the separation system, the anion of the acid used to adjust this pH, and the reaction product from which catalyst is separated (specifically the pKa of the product) were all determined as key parameters in this separation and investigation into each is discussed in more detail.

#### 4.3.2 Separation of Pd from 5-Methyl-2-phenylpyridine: Effect of pH and Acid Anion

The previous section results show acidic EDTA demonstrates effective separation of catalyst from product. However, as much of the data shows, the use of EDTA in this separation adjusts the pH of the system. In fact, Table 4.1 shows that comparable separation can be achieved using HCl instead of EDTA, but lowering the separation system to a comparable pH.

As a means of further understanding both the role of pH in this system, separations were performed with either HCl or EDTA at different pH's following the procedure in Figure 4.21 and using toluene as an anti-solvent. The results are compiled in Figure 4.27.

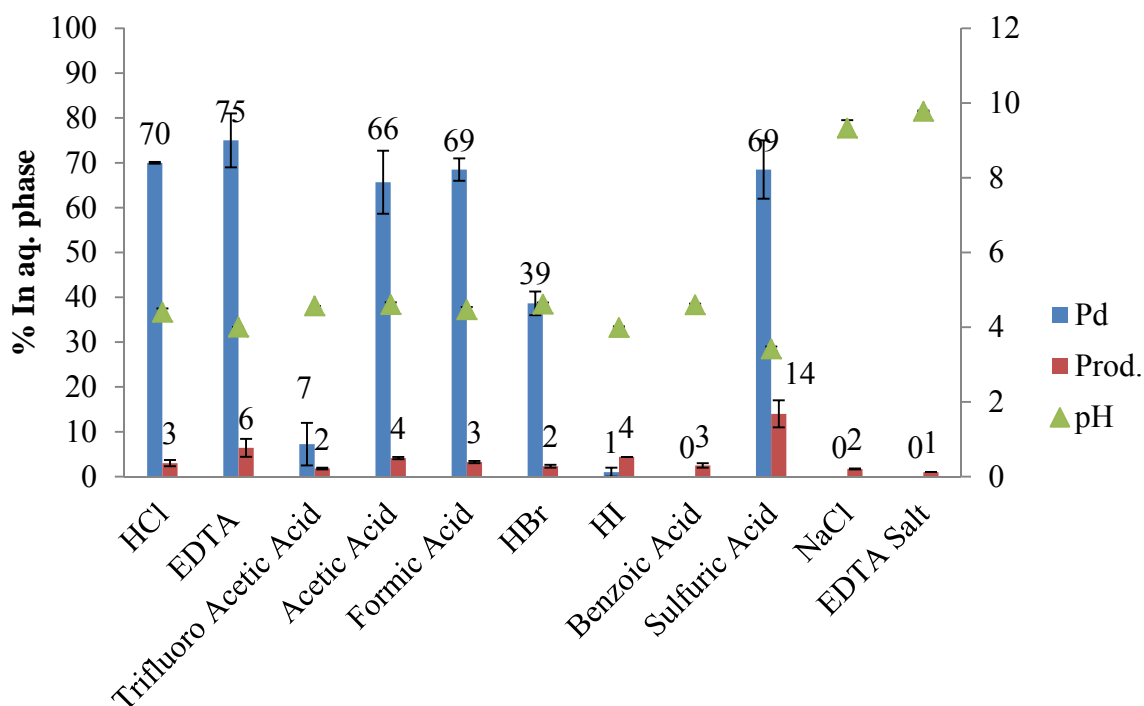


**Figure 4.27. Amount of Product and Pd in aqueous phase as a function of pH. Either HCl or EDTA used as additives. Follows separation in Figure 4.21, uses Toluene.**

Figure 4.27 shows how the amount of aqueous product and Pd vary as a function of pH using both EDTA and HCl. The amount of aqueous Pd gradually increases as pH is lowered, plateauing around 70-80% when  $\text{pH} < 5$ . At pH's  $< 3.5$ , the amount of reaction product in the aqueous phase begins increasing, reaching 70% at a pH of 2.5. This has two key implications: 1). By simply adjusting the pH to 4-5, 70-80% of the Pd can be separated into the aqueous phase with  $< 10\%$  of product present 2). the primary effect of EDTA on the separation is adjusting the pH of the system 3). When the pH is  $< 3.5$ , the amount of reaction product in the aqueous phase increases significantly.

As a means of further understanding both the role of pH and the effect of the anion of the acid in the separation of palladium from product in this system, experiments were

performed by adjusting the pH of the system to 4-5 using various acids with different anions. Additionally, experiments were done with non-acidic salts EDTA- $\text{Na}_4$  and NaCl as a comparison to the separation using acidic EDTA and HCl. Figure 4.28 shows the results of these separations.



**Figure 4.28. Summary of separation vs. pH for different additives. Pd = Palladium, Prod = 5-methyl-2-phenylpyridine.**

Separation experiments using HCl, acetic acid, formic acid, and sulfuric acid at pHs from 3.4-4.6 all give similar results to the separation using acidic EDTA (~70% of Pd in aqueous phase at a pH of ~4.0). These results show, once again, that Pd separation can be obtained in this system simply by adjusting the pH of the aqueous phase to 3.4-

4.6. Additionally, the lack of aqueous palladium in separations using EDTA- $\text{Na}_4$  and NaCl additives (pH= 9.78 and 9.33), confirms that pH is an important factor in determining the hydrophilicity of the catalyst.

Figure 4.28 also indicates that pH is not the sole factor in determining a successful separation of Pd from 5-methyl-2-phenylpyridine. Separations using HBr, HI, trifluoroacetic acid, and benzoic acid at a pH of  $\sim 4.5$  result in 36%, 0%, 7%, and 0% of Pd in the aqueous phase. The anions of these acids are all either less nucleophilic (Br, I, trifluoro acetate) or less hydrophilic (benzoate) than the cations used in successful separations. Thus, it appears that not only does pH play a key role in the separation, but the nucleophilicity and hydrophilicity of the counter-ion of the acid may also play an important part in separation.

As a means of evaluating the versatility of recycle and separation in this system using different acids, catalyst separated using HCl, acetic acid, and formic acid was recycled for use in an additional Suzuki reaction.

**Table 4.4. TOF of recycle reaction for different acids used for separation.**

Acid used for Separation	TOF at 4h
EDTA	$21 \pm 1.6$
HCl	$27 \pm 1.2$
Acetic	21
Sulfuric	31

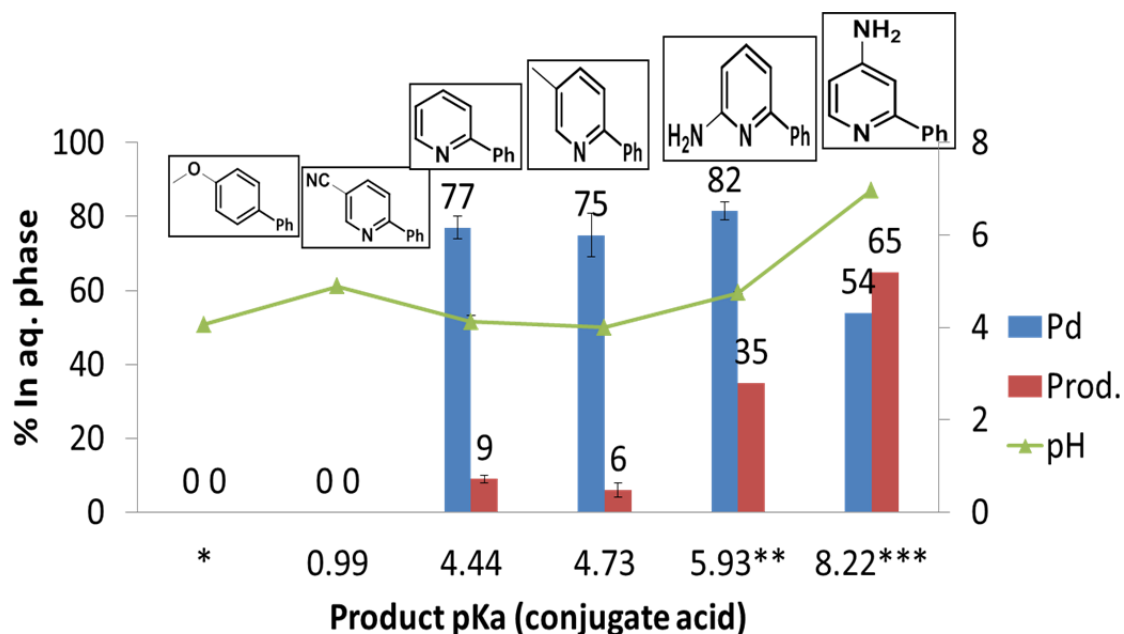


The results of recycle reactions run following separation are reported as TOF (4h) as a function of acid used for separation are shown in Table 4.4. Recycles following separation with EDTA, HCl, Acetic, and Sulfuric acid give TOF of 21, 27, 21 and 31. These values are all greater than or equal to the TOF of the fresh reaction.

### 4.3.3 Substrate Scope Expansion

#### 4.3.3.1 *Overview*

To this point, separation and recycle experiments have been performed exclusively on the system described in Scheme 4.1. It is important to test this separation and recycle technique on a wider substrate scope for several reasons. First, catalyst behavior in Suzuki reactions is highly substrate specific. Thus, a different reaction substrate could lead to different catalyst state post-reaction and affect the separation. Second, optimum Suzuki reaction pH varies with substrate as well often necessitating a different base system.<sup>25</sup> This change in base could also affect the separation technique discussed thus far. Third, more basic substrates and their Suzuki products will coordinate more strongly with palladium and lead to a more difficult separation. Finally, the different basicity of the reaction products will lead to different degrees of protonation of this product. Under the acidic conditions used in this separation technique, this could affect the product partitioning as well. For all of these reasons, the scope of Suzuki substrates was expanded in order to truly test this versatility of this technique. A non-coordinating substrate (4-bromoanisole) and pyridine substrates with products of varying basicity were chosen for investigation.

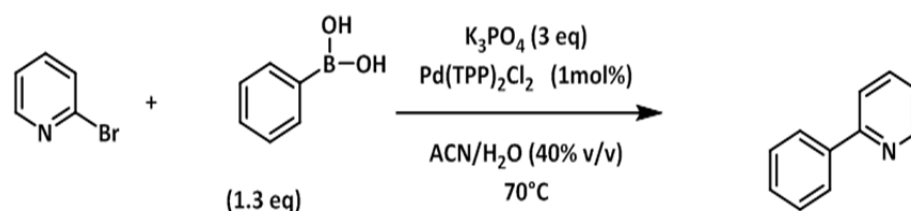


**Figure 4.29. Summary of separation vs. pH for different substrate systems. Prod (product) is pictured above result. All separations performed with 5eq EDTA. \*Product pKa unavailable. \*\*~15eq EDTA used as additive. \*\*\*1 eq. EDTA present. All compounds follow scheme in Figure 4.21 except 4-NH<sub>2</sub>-2phpyr compound.**

Figure 4.29 shows the results of these separations. All separations are performed using EDTA. At a pH of 4.1 and 4.9, separation of Pd from 4-phenylanisole and 2-phenyl-5-cyanopyridine (non-acidic and conjugate acid pKa of 0.99) using Pd both result in no Pd or product in the aqueous phase. At a pH of 4.1 and 4, separation of Pd from 2-phenylpyridine and 5-methyl-2-phenylpyridine (conjugate acid pKa of 4.44 and 4.73) result in 77% and 75% of Pd and 9% and 6% of product in the aqueous phase. Separations of Pd from 6-amino-2-phenylpyridine and 4-amino-2-phenylpyridine conjugate acid pKa of 5.93 and 8.22) at pH's of 4.8 and 7 give 82% and 54% of Pd and 35% and 65% of reaction product in the aqueous phase.

Based on this data, it appears that an interesting trend exists between the basicity of the Suzuki reaction product and the relative success of the separation. Attempts to separate Pd from the two products with essentially no basic character (the anisole and cyanopyridine) prove unsuccessful. 2-phenylpyridine and 5-methyl-2-phenylpyridine are very similar in their basicity and give very similar separation results. The more basic aminopyridines begin to show limitations in their separation due to increased amounts product in the aqueous phase. Studies of separation of Pd from each of these substrates are discussed in more detail.

#### 4.3.3.2 2-Phenylpyridine

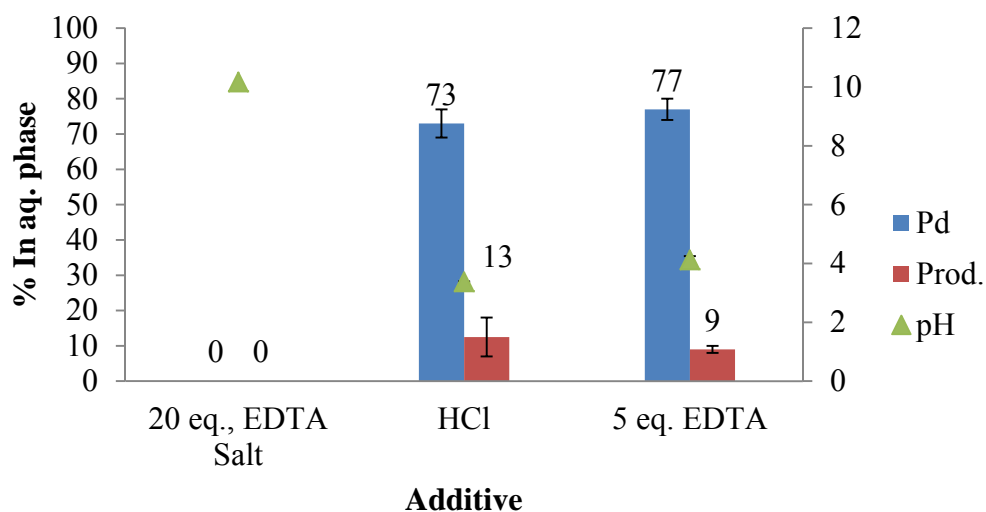


**Scheme 4.2. 2-bromopyridine reaction scheme. Reactions run for 4 hours.**

Scheme 4.2 shows the reaction scheme of 2-bromopyridine with phenylboronic acid using Pd-TPP catalyst and phosphate base in an ACN/ $H_2O$  system. The reaction reaches 80-90% yield in 2 hours. Roughly 50% of Pd is insoluble following reaction. The separation follows the procedure in Figure 4.21. This substrate was examined for the reaction product has a similar  $pK_a$  (4.44) to 5-methyl-2-phenylpyridine (4.73), and, thus, should have the same degree of coordination with the Pd catalyst and similar hydrophilicity at a comparable pH. Figure 4.29 shows that separation of Pd from 2-phenylpyridine gives very similar results, 77% Pd and 9% product in the aqueous phase,

to separations of Pd from 5-methyl-2-phenylpyridine (75% and 4%) using EDTA at similar pH's (4.1 and 4.0).

Figure 4.30 compares the separation of Pd from product to separations using HCl and EDTA- $\text{Na}_4$  salt. These separations give 73% and 0% of Pd and 13 and 0% of product in the aqueous phase at pHs of 3.4 and 10.2. The results agree with the separation of Pd from 5-methyl-2-phenylpyridine using these compounds and indicate that adjusting the pH of the separation system using the appropriate acid results in separation of Pd from reaction product.



**Figure 4.30. Separation of 2-phenylpyridine as a function of Additive. Separation procedure follows Figure 4.21.**

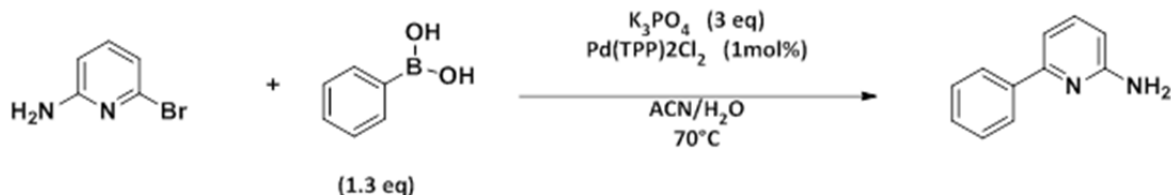
Experiments were also performed to recycle Pd separated from this substrate. The recycle reaction follows the procedure in 4.2.2.11. Results are shown in Table 4.5.

**Table 4.5. Recycle reaction of Pd separated from 2-phenylpyridine compared to fresh reaction. The additive used for separation is listed. The amount of TPP added to the reaction system is listed as well**

Additive for Separation	Eq. TPP added to Recycle	TOF (2 h)
None (fresh reaction)	2 (Pd(TPP) <sub>2</sub> Cl <sub>2</sub> )	46 ± 0
EDTA	5	0
EDTA	20	59
HCl	20	56

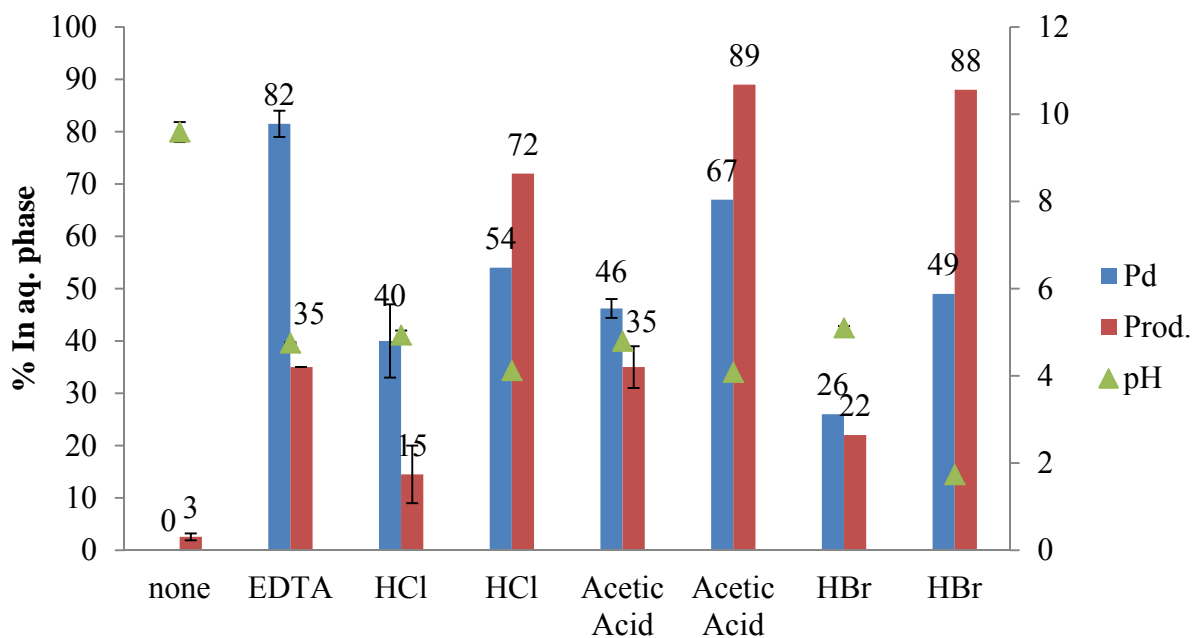
Table 4.5 compares the TOF of different recycle reactions for Pd separated from 2-phenylpyridine. When only 5eq of TPP are added, no reactivity is seen. Recycle reactions where 20eq TPP are added prior to recycle give TOF values of 59 and 56 when EDTA and HCl are additives used to perform the separation. All Pd is soluble following reaction. This data indicates that Pd separated from this substrate shows a higher degree of reactivity than in the fresh reaction (TOF = 46, 1 mol% loading). This is due to the insolubility of the Pd in fresh reactions, but also could be an indication that a portion of the soluble catalyst in the fresh reaction is inactive. This was probed by running a fresh reaction run with 0.5 mol% (half) loading. This reaction gives a TOF of 56 (similar to recycle reactions) and all Pd remains soluble. These results indicate that there is a decline in catalyst activity and solubility as catalyst loading increases past 0.5mol%.

#### 4.3.3.3 6-Amino-2-phenylpyridine



**Scheme 4.3. Reaction of 6-amino-2-bromopyridine with phenylboronic acid.**

Scheme 4.3 shows the reaction schemes for the reaction of 6-amino-2-bromopyridine with phenylboronic acid in ACN/ $H_2O$  solvent with a Pd-TPP catalyst. The reaction reaches 60% yield in 4 hours. This substrate was chosen for investigation due to the higher basicity of the reaction product ( $pK_a = 5.93$ ) compared to 5-methyl-2-phenylpyridine. The higher basicity of this substrate offers challenges in separation of Pd from product due to 1) increased coordination with catalyst and 2) increased protonation, and, therefore, hydrophilicity of the product at lower pH. The separation of catalyst from 6-amino-2-phenylpyridine follows the procedure in Figure 4.21.



**Figure 4.31. Acidic separation of Pd from 6-amino-2-phenylpyridine. Follows procedure in figure**

Figure 4.31 shows the results of separating Pd from 6-amino-2-phenylpyridine reaction product. At a pH of 9.6, separation with no additive gives 0% and 3% of palladium and product in the aqueous phase. Separation with EDTA at a pH of 4.8 gives 82% of Pd and 35% of reaction product in the aqueous phase. The use of HCl as an additive gives 40% of Pd and 15% of product in the aqueous phase at a pH of 4.9. Lowering the pH to 4.1 with HCl gives 54% of Pd and 72% of product in the aqueous phase. A separation with acetic acid at a pH of 4.8 gives 46% of Pd and 35% of product in the aqueous phase. When acetic acid is used to lower the pH to 4.1, Pd and reaction product are found in the aqueous phase in the amounts of 67% and 89%, respectively. Separations performed with HBr at pHs of 5.1 and 1.7 give 26% and 49% aqueous Pd and 22% and 88% aqueous product.

These separation results differ from the separation of Pd from 5-methyl-2-phenylpyridine. At a similar pH, EDTA gives comparable amounts of aqueous Pd; however, the amount of reaction product is higher in the case of 6-amino-2-phenylpyridine. This is likely due to increased protonation of this more basic reaction product. The effect of the basicity of the reaction product on its separation is evident by the >70% of aqueous product seen when the pH of the system is dropped to <4.1. Interestingly, comparable (to 5-me-2-phenylpyridine system) aqueous Pd amounts are not seen with HCl and acetic acid separations. This could be an indication that chelation ability plays a larger role when more basic reaction products are used. Separations with HBr show the same lack of success seen when it is used in the 5-methyl-2-phenylpyridine system.

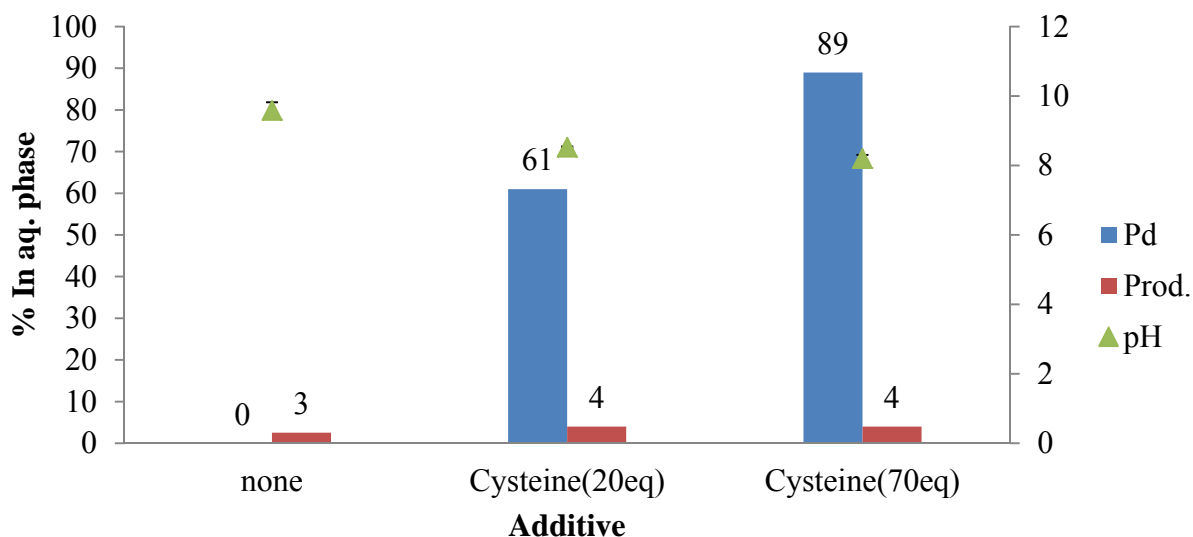
Following separation using EDTA, the separated Pd was recycled accord to the procedure in 4.2.2.11. The results are shown in Table 4.6.

**Table 4.6. Summary of recycle reactions run for Pd separated from 6-amino-2-phenylpyridine**

<b>Condition</b>	<b>Eq. TPP added prior</b>	<b>TOF (4 hour)</b>
Fresh Reaction	Fresh reaction	15
Separated 20 eq. EDTA	0	3.3
Separated 20eq. EDTA	5	8.4



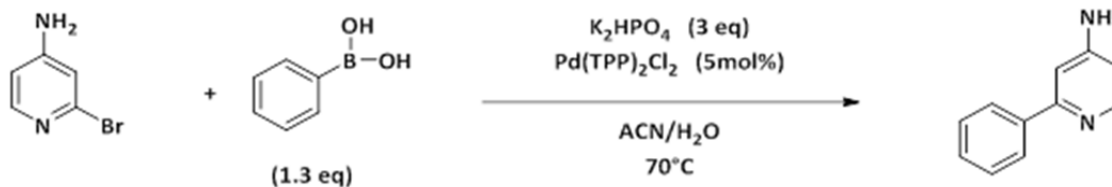
Recycle reactions run with 0 and 5 eq. of TPP added following separation give TOF of 3.3 and 8.4. Both values are lower than the TOF seen in the fresh reaction (15). The lower reactivity could be due to the large amount of reaction product recycled with the catalyst. This basic compound could potentially coordinate with the catalyst, thus slowing the reactivity.



**Figure 4.32. Separation of Pd from 6-amino-2-phenylpyridine using cysteine as an additive. Prod: 6-amino-2-phenylpyridine.**

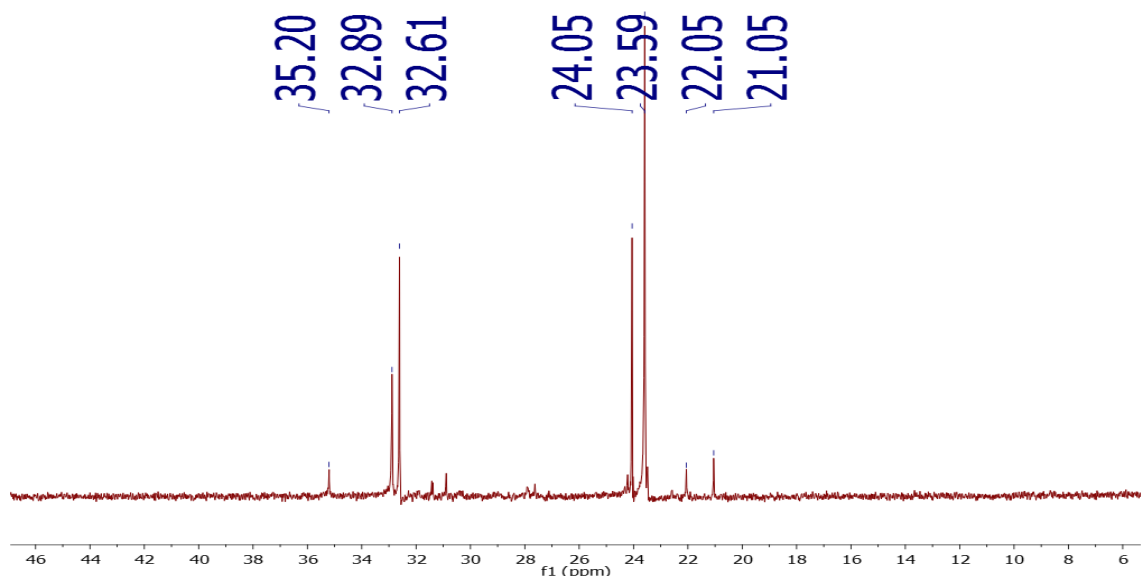
Figure 4.32 shows separation experiments where cysteine was used as an additive to separate Pd from 2-amino-6-phenylpyridine. 20 eq. and 70eq. of cysteine give 61% and 89% of Pd in the aqueous phase, and 4% of product in the aqueous phase. These separations occur at pHs of 8.5 and 8.2. These results indicate that effective separation of Pd from this reaction product is possible at less-acidic pH's using a cysteine, which is a sulfur-containing chelant.

#### 4.3.3.4 4-Amino-2-phenylpyridine



**Scheme 4.4. Reaction scheme for Suzuki coupling of 4-amino-2-phenylpyridine with phenylboronic acid.**

Scheme 4.4 shows the reaction scheme for the reaction of 4-aminopyridine with phenylboronic acid in ACN/ $H_2O$  solvent, using Pd-TPP catalyst (5 mol% loading). The reaction reaches 80-90% yield in 24 hours. This substrate was chosen for investigation due to the higher basicity of the reaction product (conjugate acid  $pK_a = 8.22$ ) compared to 5-methyl-2-phenylpyridine. The higher basicity of this substrate offers challenges in separation of Pd from product due to 1) increased coordination with catalyst and 2) increased protonation, and, therefore, hydrophilicity of the product at lower pH.

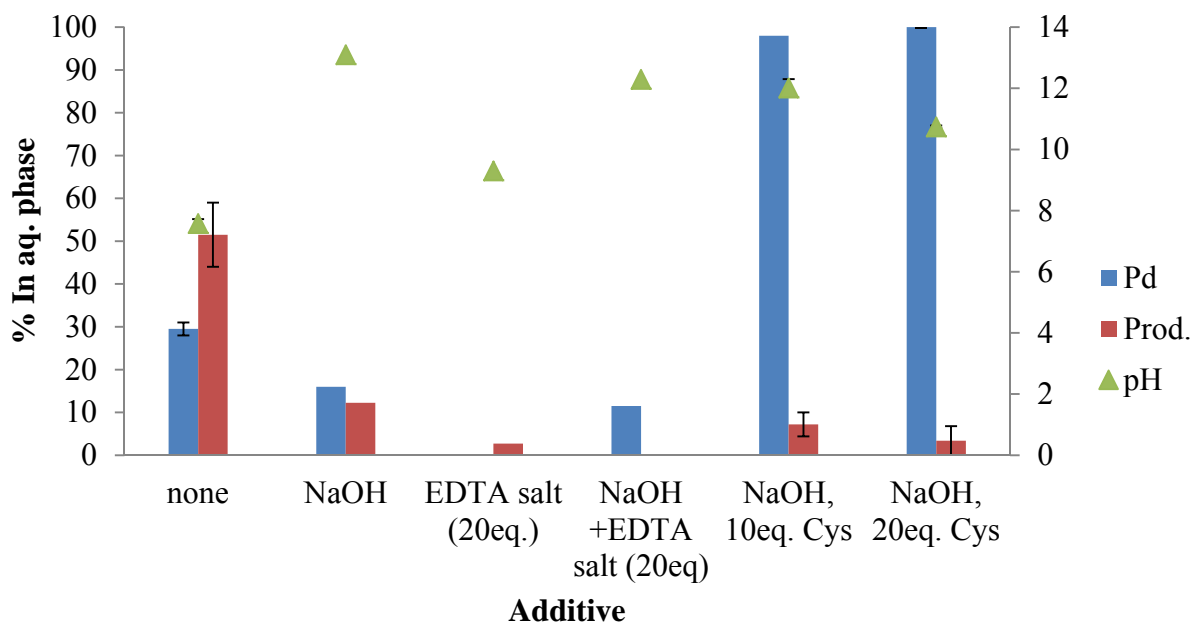


**Figure 4.33. Post-reaction  $^{31}\text{P}$ -NMR Scheme 4.4.**

Figure 4.33 shows the P-NMR following Suzuki reaction of 4-amino-2-bromopyridine. The peaks in the 30-35 ppm range are indicative of oxidized phosphine, while those in the 20-25ppm range indicate Pd-bound phosphine. The presence of phosphine bound to Pd could make separation of Pd into the aqueous phase more difficult.

Ultimately, separation of Pd from 4-amino-2-phenylpyridine proved to be challenging due to the basicity of the product. The product is so hydrophilic that separations could not be performed using a wash step (due to product losses in the aqueous phase), thus the separation follows the process in Figure 4.14. The separation of catalyst from 4-amino-2-phyridine at pH 6.97 (EDTA) gives aqueous amounts of 54% Pd and 65% product (Figure 4.29). Considering the higher pH of the system (compared to

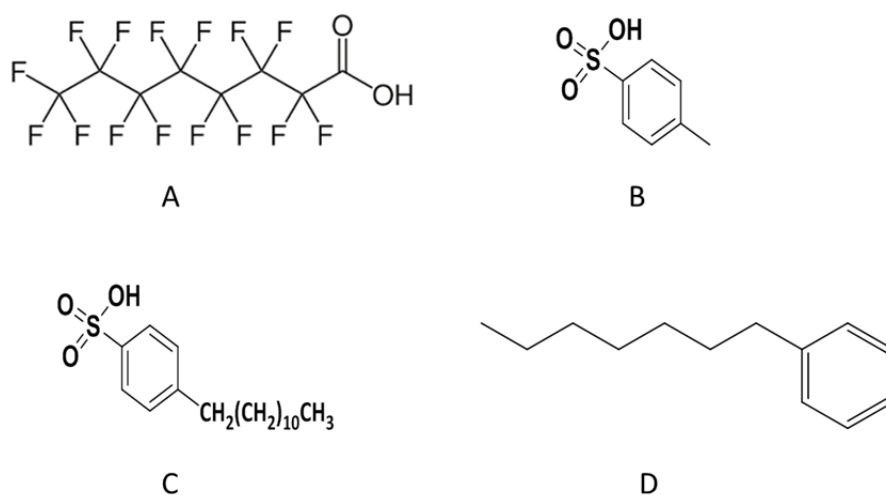
other substrates examined), the amount of aqueous Pd is significant; however, the amount of aqueous product provides results in poor separation and a limitation in this separation.



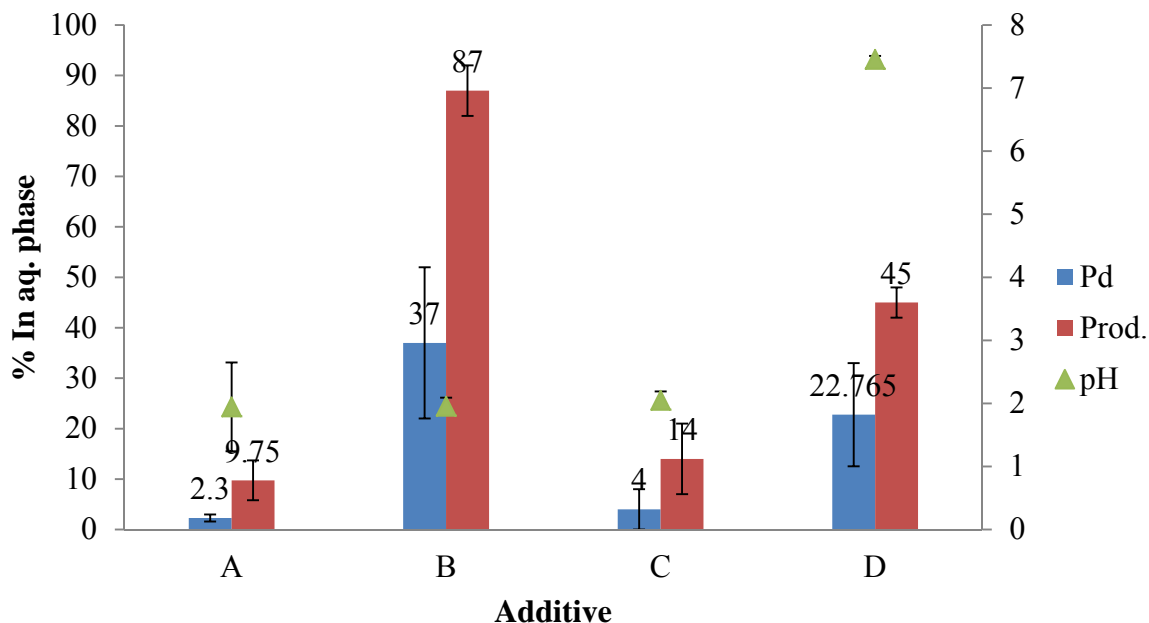
**Figure 4.34. Separation of Pd from 4-amino-2-phenylpyridine under basic conditions using toluene as an anti-solvent. Prod: 4-amino-2-phenylpyridine.**

Figure 4.32 shows the results of separating Pd from the Suzuki reaction product 4-amino-2-phenylpyridine under basic ( $\text{pH} > 10$ ) conditions. NaOH is used to adjust the pH of the separation system of the different trials. When no additive is used, the aqueous phase has a pH of 7.6 and 30% and 52% of Pd and reaction product respectively is seen in the aqueous phase. When NaOH is used to adjust the pH of the system to 13.1 the amount of aqueous Pd and product drop to 16% and 12%, respectively. The addition of 20eq. of EDTA salt gives 12% Pd and no product in the aqueous phase. As seen with

other substrates, effective separation with EDTA is ineffective at a higher pH. Effective separation can be achieved by the addition of cysteine at a higher pH however. Separations using 10 and 20 equivalents of cysteine at pHs of 11.7 and 10.7 give 98% and 100% of Pd and 4.4% and 3.4% of reaction product in the aqueous phase. While this demonstrates the separation can be achieved with this system, the use of cysteine likely means the recycle of separated Pd will be unsuccessful.



**Figure 4.35. Hydrophobic acid additives used. A: perfluorooctanoic acid, B: paratoluene sulfonic acid C: Dodecylbenzenesulfonic acid. D: Heptylbenzene**

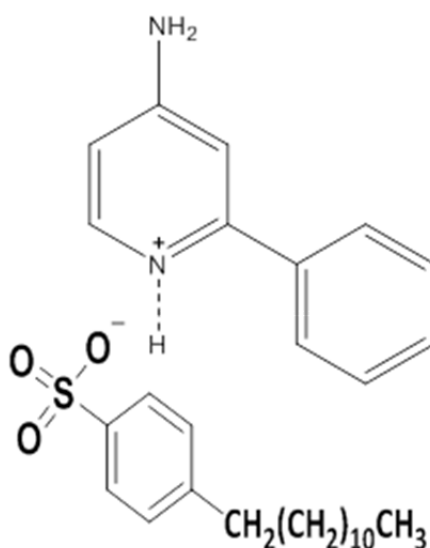


**Figure 4.36. Separation of Pd from 4-amino-2-phenylpyridine using hydrophobic acidic additives. Prod: 4-amino-2-phenylpyridine. A, B, C, and D refer to additives in Figure 4.35.**

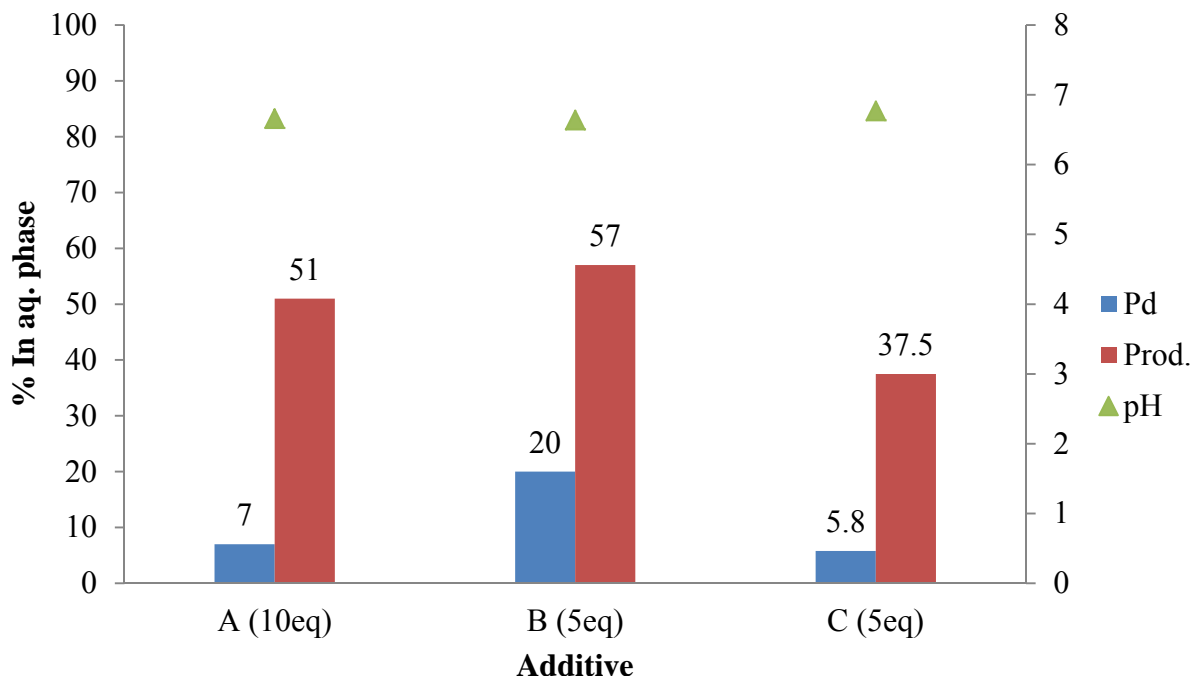
As a means of testing the effect of hydrophobic additives on both Pd and reaction product partitioning, several hydrophobic additives (Figure 4.36) were added to the separation system. Three of the additives (A-C) were acidic, while D was non-acidic, but still very hydrophobic. Separations with 20eq. of A, B, and C were performed at pHs of 1.2, 1.8, and 1.9. These separations gave 3%, 52%, and 0% of Pd in the aqueous phase. The same separations gave 14%, 92%, and 7% of reaction product in the aqueous phase. A separation with non-acidic heptylbenzene (D) is performed at a pH of 7.4 and results in 13% and 42% of aqueous Pd and product.

Interestingly, the use A and C results in the system reaching a low pH, yet the basic product remains in the organic phase. B does not show this same effect. Based on

the halogenated chain of compound A and the longer, hydrocarbon chain of compound C, A and C are likely much more hydrophobic than additive B. There are two possible reasons that reaction product (and Pd) partitioning behaves the way they do in their presence. 1). The strong hydrophobicity of these additives influences the phase behavior to make the reaction product and Pd favor the organic phase. The results with additive D do not support this theory, however. D is also a very hydrophobic additive, so, presumably very little reaction product would be seen in the aqueous phase if the primary additive effect was phase behavior. The more likely phenomena is that 2). The hydrophobic additive anion coordinates with the protonated reaction product (Figure 4.37). Considering the system uses a 5 mol% catalyst loading, 20eq. of an additive is a stoichiometric equivalent to the amount of product in the system and could coordinate with a large portion of the reaction product.



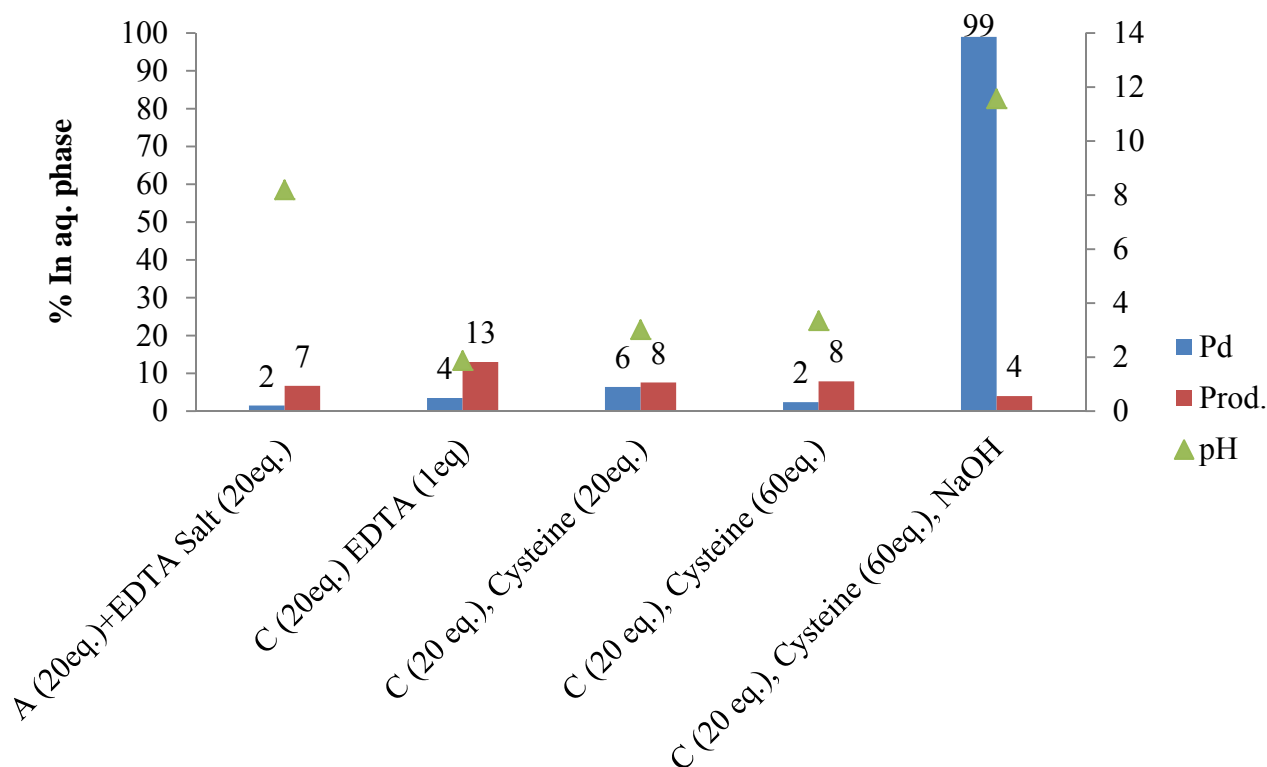
**Figure 4.37. Behavior of protonated product with hydrophobic additives.**



**Figure 4.38. Separation of Pd from 4-amino-2-phenylpyridine using hydrophobic additives at higher pH. A, B, and C refer to additives in Figure 4.35.**

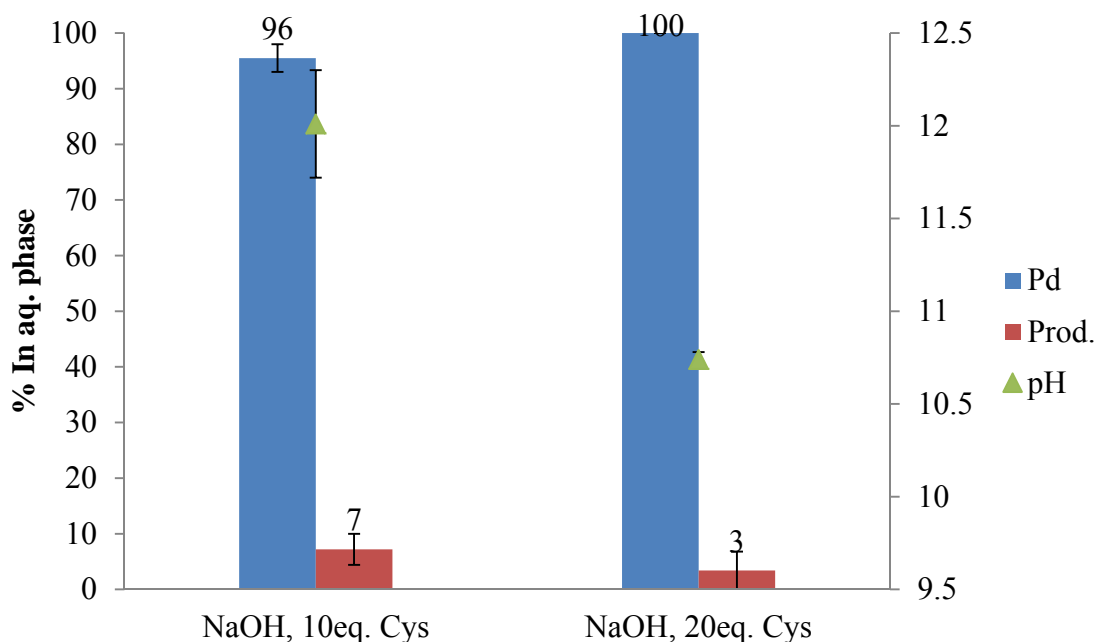
As a means of testing the effect of additive loading on separations using hydrophobic additives, separations were run with fewer additives. Figure 4.38 shows separation results using hydrophobic additives A, B, and C at pHs of 6.7, 6.6, and 6.8. These separations give 7%, 20%, and 6% of Pd in the aqueous phase and 51% 57% and 38% of reaction product in the aqueous phase. It is interesting that in the case of A and C, despite being at a higher pH than in Figure 4.36 (pH of 1.2 and 1.9) there is significantly more product in the aqueous phase (51% and 38% compared to 14% and 7%). Considering there is less additive present at these higher pHs, this supports the theory of product partitioning proposed in Figure 4.37.





**Figure 4.39. Separation of Pd from 4-amino-2-phenylpyridine using DBSA and chelating additive. A and C refer to additives in Figure 4.35.**

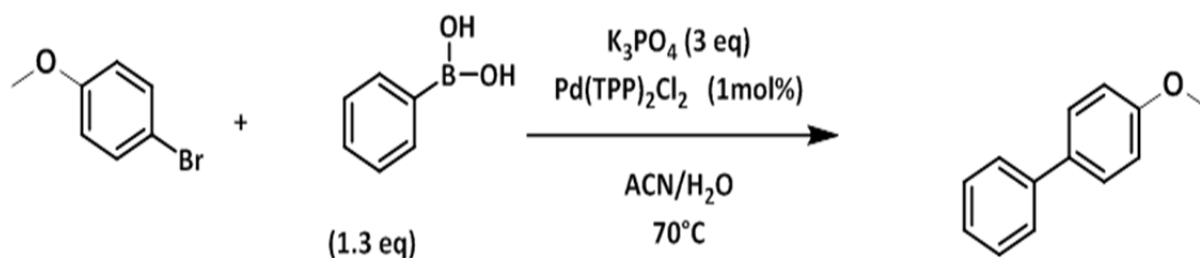
Figure 4.39 shows further study of separation using A and C in conjunction with chelating additives. Separations using 20 eq. EDTA and 20eq. A, 1 eq. EDTA and 20eq. C, 20eq. Cysteine and 20eq. C, and 60eq. Cysteine with 20eq. C give poor separation with 2%, 4%, 6% and 2% Pd and 7%, 13%, 8%, and 8% product in the aqueous phase. However, when NaOH is used to raise the pH (and likely deprotonate the DBSA) to 11.6, 99% of Pd and 4% of product is seen in the aqueous phase. Based on this result, separations were performed using only base and cysteine.



**Figure 4.40. Separation of Pd from 4-amino-2-phenylpyridine using cysteine and base.**

The results of using base and cysteine to separate Pd from reaction product are shown in Figure 4.40. When 10 eq. of cysteine is used at a pH of 12, 96% of Pd and 7% of product are found in the aqueous phase. When 20 eq. of cysteine is used at a pH of 10.7, 100% of Pd and 3% of product are found in the aqueous phase. These results indicate that using cysteine, at a high enough pH (>10), Pd can effectively be separated into the aqueous phase while keeping reaction product in the organic phase. This is likely due to the strong chelation ability of cysteine and the fact that the pH is basic enough to prevent a significant amount of product from becoming protonated. Attempts to recycle separated Pd were unsuccessful.

#### 4.3.3.5 4-Phenylanisole



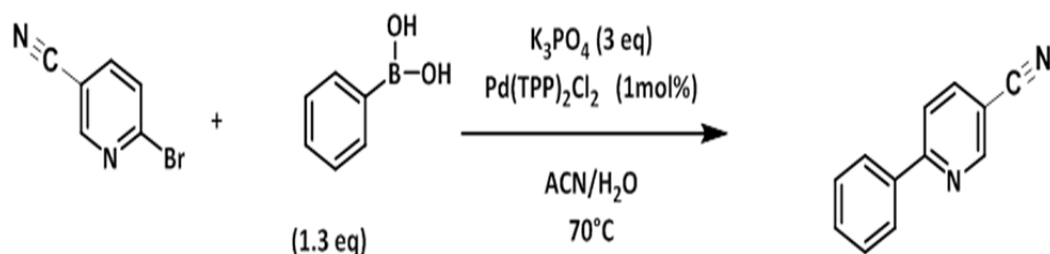
**Scheme 4.5. Suzuki Reaction of 4-bromoanisole**

Scheme 4.5 shows the reaction scheme for the reaction of 4-bromoanisole and phenylboronic acid in ACN/ $H_2O$  solvent, using Pd-TPP catalyst. The reaction reaches >90% yield within 20 minutes. This substrate was chosen for investigation due to the lack of basicity (and, therefore their unlikelihood to coordinate to Pd) of the reaction product. In theory, this should result in an easier separation. Separation follows the scheme in Figure 4.21 using acidic EDTA. Separation of these two substrates following reaction gives no measurable amount of product or Pd in the aqueous phase at pHs of 4.06 and 4.89. The lack of product in the aqueous phase is unsurprising, given the lack of basicity, and, therefore, minimal amount of protonation of the two products. The lack of aqueous Pd is more difficult to explain, for, at similar pH's, separations from other reaction products (Figure 4.29) give a significantly higher amount of aqueous Pd.

A potential explanation is the lack of oxidation of TPP during reaction (30% is oxidized), as this has been seen to reduce hydrophilicity of Pd under separation

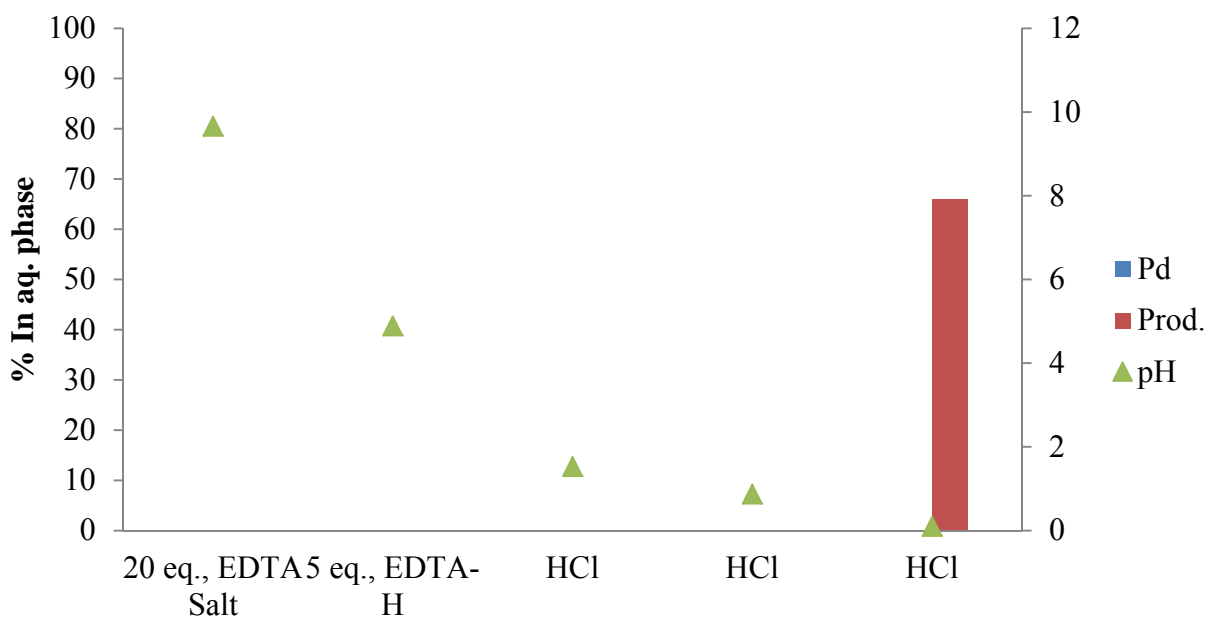
conditions (Table 4.2). The reaction undergoes significant darkening which could be an indication of Pd nanoparticle formation (not seen in reactions using more basic substrates). Nanoparticle formation could make moving Pd into the aqueous phase more difficult.

#### 4.3.3.6 5-Cyano-2-phenylpyridine



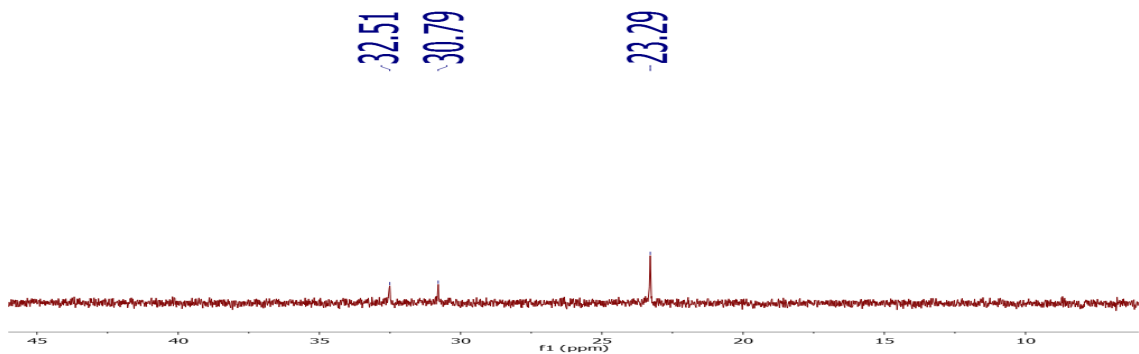
**Scheme 4.6. Suzuki reaction of 5-cyano-2-phenylpyridine.**

Scheme 4.6 shows the reaction scheme for the reaction of 5-cyano-2-bromopyridine with phenylboronic acid in ACN/ $H_2O$  solvent, using Pd-TPP catalyst. The reaction reaches >90% yield within 20 minutes. This substrate was chosen for investigation due to the lack of basicity (and, therefore their unlikelihood to coordinate to Pd) of the reaction product. In theory, this should result in an easier separation



**Figure 4.41. Separation data for separation of Pd from 5-cyano-2-phenylpyridine. Separation procedure uses wash step. Shows amount of aqueous product and Pd. Prod: 5-cyano-2-phenylpyridine.**

Figure 4.41 shows the amount of aqueous Pd when non-acidic EDTA, acidic EDTA, and HCl are used as additives. For both EDTA separations (pH of 9.66 and 4.89), no Pd or reaction product is seen in the aqueous phase. Separations are performed with HCl at pHs of 1.5, 0.9, and 0.1. At each of these pHs, no Pd is seen in the aqueous phase. No product is seen in the aqueous phase except for the separation performed at pH = 0.1. This gives an aqueous product amount of 66%. The Pd results agree with those seen in previous separations of Pd from 4-phenylanisole.

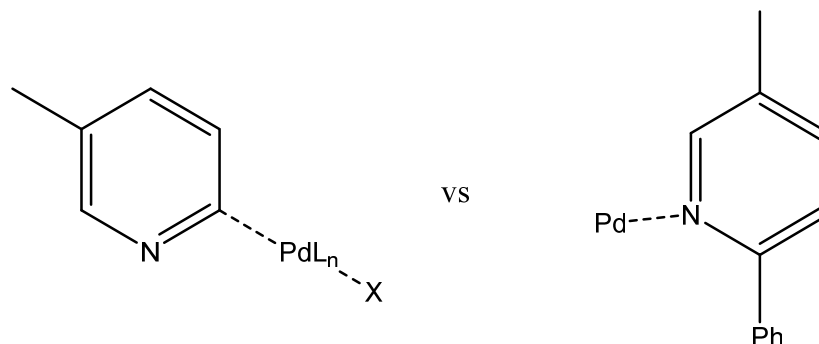


**Figure 4.42.  $^{31}\text{P}$ -NMR of organic phase following reaction.**

Figure 4.42 shows the  $^{31}\text{P}$ -NMR of the organic phase of following reaction in Scheme 4.6. Peaks at 32.5 and 30.8 are indicative of TPP-O complexes while the peak at 23.3 indicates the presence of Pd-bound phosphine. Table 4.2 indicates that TPP plays a role in the separation of Pd into the aqueous phase, thus the presence of Pd-bound phosphine post-reaction may be detrimental to separation of Pd.

As a means of understanding the unsuccessful separations with this substrate, the role that starting material/reaction product plays on post-reaction catalyst state and how that may affect the separation of Pd was examined. Reactions and subsequent separations were run with 5-cyano-2-bromopyridine in the presence of both 5-methyl-2-bromopyridine and 5-methyl-2-phenylpyridine. These experiments would result in the Pd catalyst entering into the catalytic cycle with the 5-methyl-2-bromopyridine substrate both during and following reaction of the cyano substrate. This could then result in 1). Catalyst inserted into the methyl substrate following the reaction and 2). Potential stabilization of the catalyst through the ligation from the more basic 5-methyl-2-

phenylpyridine reaction product, reducing nanoparticle formation and loss of Pd from Pd-black (Scheme 4.7).



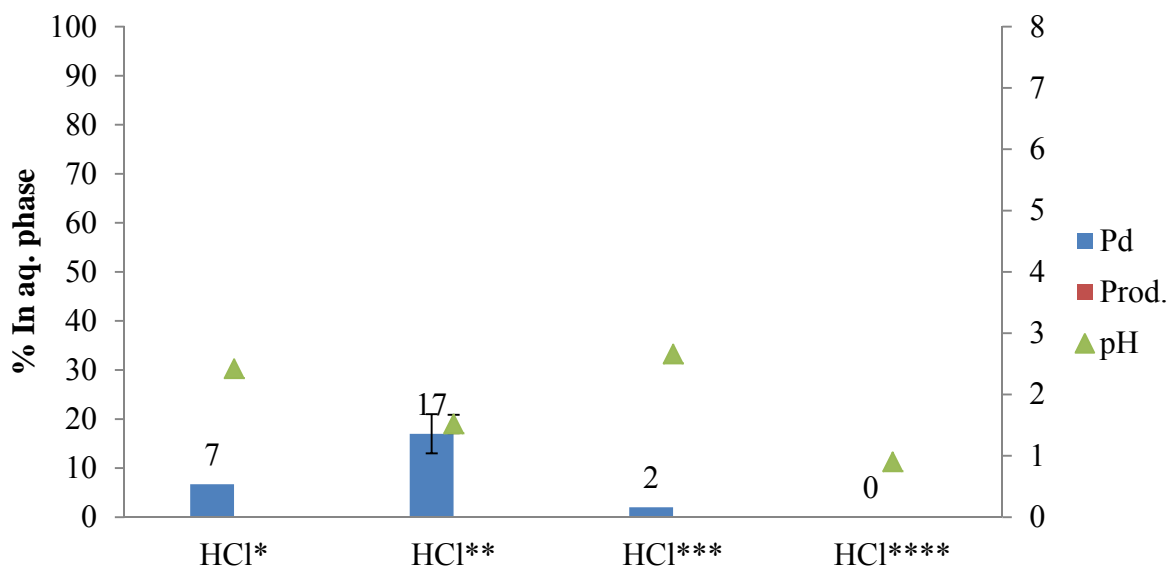
**Scheme 4.7. Potential effect of having 5-methyl-2-bromopyridine present in Suzuki reaction.**

1). 0.2 eq. of 5-methyl-2-bromopyridine was added when the reaction reached temperature. After 10 minutes, quantitative amounts of 5-cyano-2-phenylpyridine are formed. The reaction was then stopped after an additional 10 minutes, due to significant darkening of the reaction. At this point, 70% of Pd remained in solution and 8% yield of 5-methyl-2-phenylpyridine was formed.

2). To avoid issues of loss of catalyst and ensure Pd had the chance to enter into the catalytic cycle. The experiment was repeated, but 0.2 eq. of 5-methyl-2-bromopyridine was added to the reaction system from the beginning. Quantitative yields of 5-cyano-2-phenylpyridine are achieved quickly (<1hr). The reaction was then allowed to proceed for 5 hours to ensure Pd entered into the catalytic cycle (38% 5-methyl-2-phenylpyridine product achieved). 86% of Pd remains soluble in the organic phase. Separations of both of these experiments were carried out using HCl.

3). The equivalent amount of 5-methyl-2-phenylpyridine formed in (2).) is added at the beginning of the reaction and the reaction is run for 15 minutes. Full yield of the cyano product is reached and 87% of the Pd remains in the solution following the reaction.

All of these separations were performed with HCl.



**Figure 4.43. \*added at reaction temperature. \*\*SM present from beginning. \*\*\*product from beginning. \*\*\*\*SM after wash step.**

Figure 4.43 shows that, when 5-methyl-2-bromopyridine is add to reaction at temperature, 7% of Pd and no reaction product is found in the aqueous phase. When the starting material is present in the reaction initially, 17% of Pd and 0% of reaction product is present in the aqueous phase at a pH of 1.5. When 5-methyl-2-phenylpyridine (reaction product) is present initially in the reaction 2% of Pd and 0% of product are present in the



aqueous phase during separation. Adding the starting material following reaction results in no aqueous Pd or product.

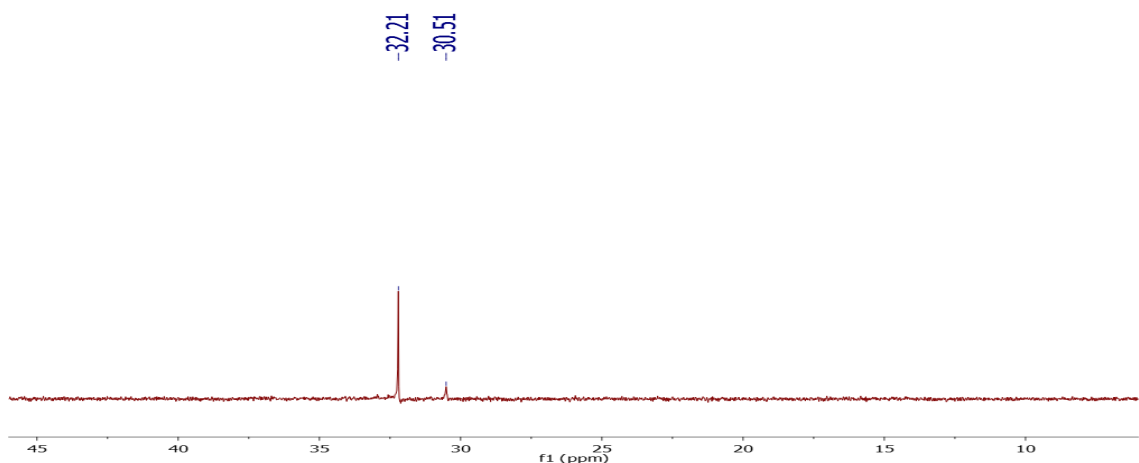
While this data could indicate that the addition of 5-methyl-2-bromopyridine helps separate Pd as a result of catalyst insertion into the species (as opposed to stabilization by the reaction product, Scheme 4.7), it is important to examine phosphine oxidation in each of these reactions, for the presence of TPP has been shown to effect the separation of Pd from reaction product (Table 4.2).

**Table 4.7. Separation of Pd from 5-cyano-2-phenylpyridine. SM = 5-methyl-2-bromopyridine. Prod = 5-methyl-2-phenylpyridine. Separations carried out using HCl.**

Condition	Reaction Time(h)	% TPP Oxidized	%Pd in aq.	pH
Typical Reaction	heat to temperature	30	0	1.5
SM added at temperature	0.25	30	7	2.4
SM present initially	5	100	17	1.5
Product Present initially	0.25	46	2	2.7

Table 4.7 summarizes the separation data in Figure 4.43. In a typical Suzuki reaction of 5-cyano-2-bromopyridine (no methylpyridine added), 30% of TPP is oxidized and no Pd is seen in the aqueous phase during separation. When the methylpyridine starting material is added when the reaction temperature, 30% of TPP is oxidized and 7% of aqueous Pd is seen during separation. When methylpyridine is present initially and the reaction is run for longer time periods, 17% of Pd is found in the aqueous phase during separation. Finally, when methylpyridine reaction product is added to the system, 46% of

TPP is oxidized and 2% of aq. Pd is seen in the aqueous phase during separation. This data indicates that the primary benefit of 5-methyl-2-bromopyridine in this reaction is actually the increased stabilization of soluble Pd, which allows for longer reaction time and greater oxidation of TPP ligand. TPP has been shown to increase organic-phase Pd retention during separation (Table 4.2), thus greater oxidation can help to improve Pd separation.

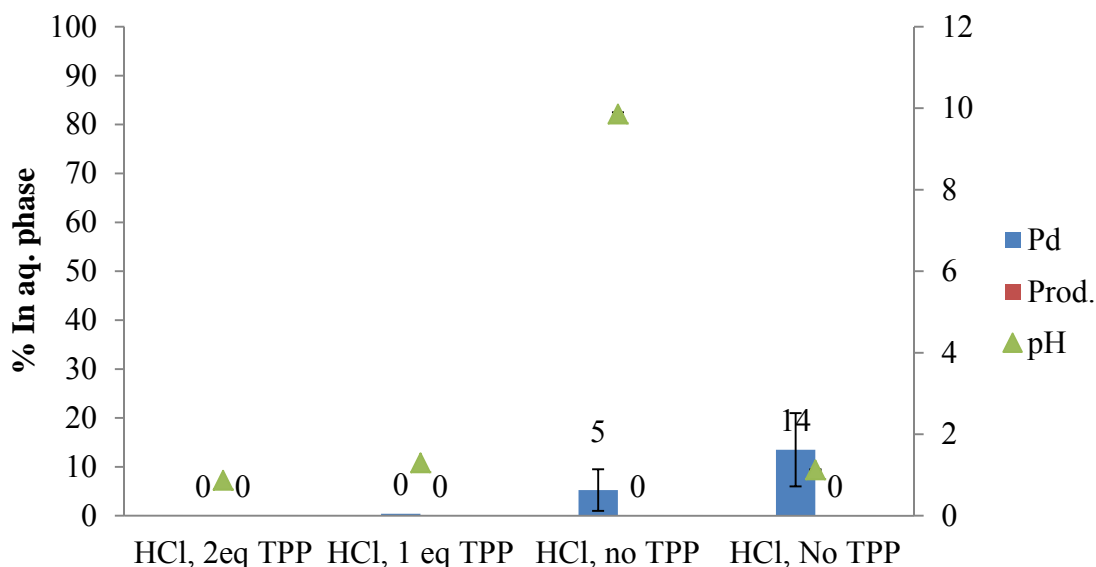


**Figure 4.44. Post-reaction  $^{31}\text{P}$ -NMR of Table 4.7 (SM present initially.)**

Figure 4.44 shows the post-reaction  $^{31}\text{P}$ -NMR of when 5-methyl-2-bromopyridine is present initially (Table 4.7). Both peaks are indicative of TPP-O species and there is no evidence of Pd-bound phosphine, confirming GC data in Table 4.7 and giving a possible explanation of the improved separation.

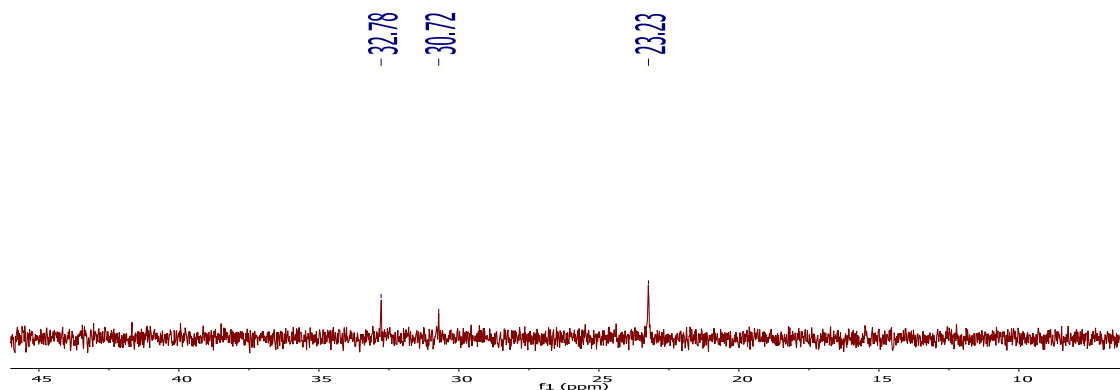
As a means of testing this theory, reactions were run following Scheme 4.6, but using  $\text{PdCl}_2$  as catalyst with 1 and 0 eq. of TPP added. The reactions are heated to

temperature and then reaction is stopped. The reaction yields are 40% and 50%, respectively. Separation is then carried out according to the process in Figure 4.21 and HCl is used to adjust separation pH. Results are shown in Figure 4.45.



**Figure 4.45. Separations with varying amounts of TPP present in reaction.**

When reactions are run with 1eq. of TPP, 60% of TPP is oxidized. The resulting separation gives no Pd in the aqueous phase. When no TPP is present in the reaction system, separations at pH of 9.9, 1.1 and 0.15 give 5%, 14%, and 23% of aqueous Pd during separation. These separations indicated the amount of unoxidized TPP reduces the hydrophilicity of Pd during separation and explains part of the difficulty in separating catalyst from this reaction system.



**Figure 4.46. Post-reaction  $^{31}\text{P}$ -NMR of reaction when 1 eq. TPP is present.**

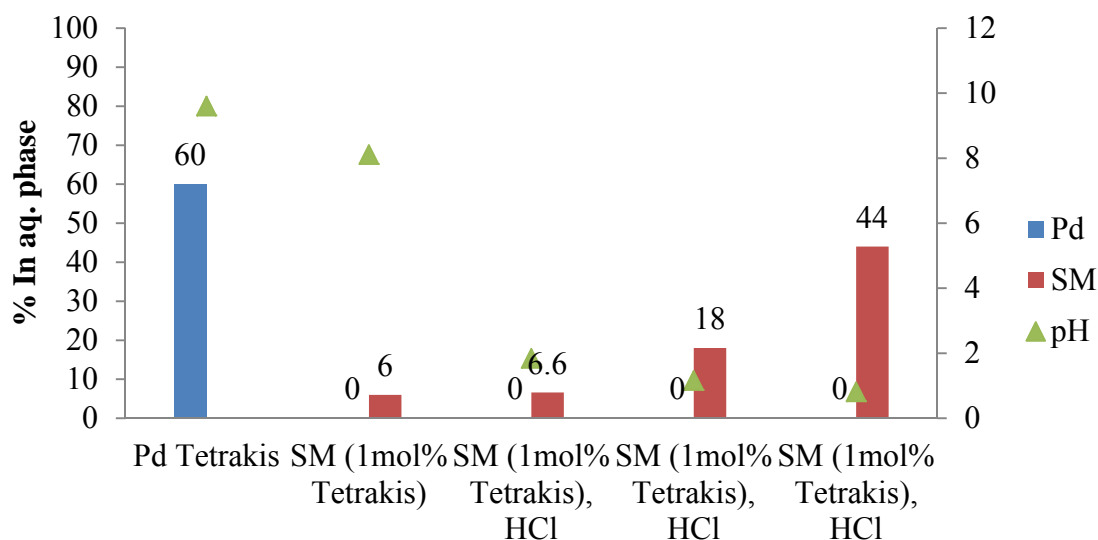
The post-reaction  $^{31}\text{P}$ -NMR when 1 eq. TPP is present confirms that a significant of TPP is still bound to Pd (Figure 4.46, peak at 23.2 ppm), thus this could explain why no aqueous Pd is seen during separation conditions (Figure 4.45).

The lack of aqueous Pd during separation when no TPP is present (compared to separation from more basic pyridines) indicates that the presence of Pd-bound phosphine is not the sole reason that Pd cannot be separated following reaction of 5-cyano-2-bromopyridine. The darkening of the reaction indicates the possibility of nanoparticle formation which could be another reason that separation is difficult.

Finally, separation of Pd following reaction in Scheme 4.6 is successful using cysteine. At pH = 8.8, 20 eq. of cysteine gives 98% of Pd and 0% of reaction product in the aqueous phase.

#### 4.3.4 Control Separations – 5-Methyl-2-phenylpyridine

As a means of further illuminating the role the starting material, product, and phosphine ligand on separation of Pd from reaction product, several “control separation” experiments were run. This section discusses those results.



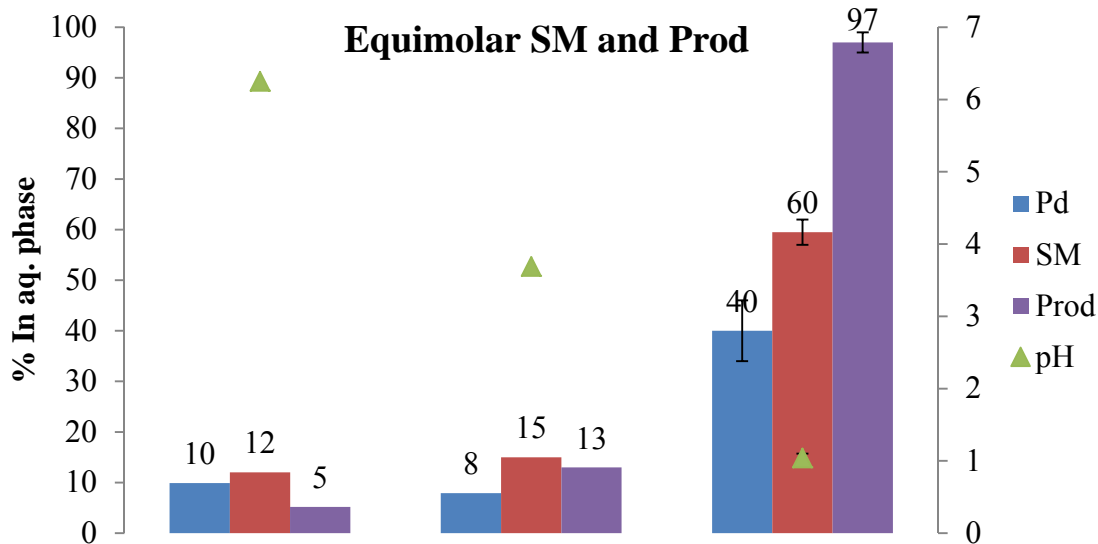
**Figure 4.47. Control separation with Pd-tetrakis. SM= 5-methyl-2-bromo-pyridine.**

Figure 4.47 shows results of control separations with Pd(TPP)<sub>4</sub> (Pd-tetrakis) and 5-methyl-2-bromopyridine. Water, acetonitrile, and toluene are added in a proportion meant to mimic that of the post-reaction separation experiments. 0.3M 5-methyl-2-bromopyridine, 1mol% Pd tetrakis, and HCl are added to adjust reaction parameters. The Pd-tetrakis is chosen as a Pd(0) source which could potentially insert in the starting material. HCl is used to adjust the pH and potentially partitioning of the pyridine and Pd.

When only Pd-tetrakis is added, 60% of soluble catalyst is found in the aqueous phase. The addition of starting material results in 0% Pd and 6% Pd in the aqueous phase.

This could be an indication the Pd is inserted into the starting material. However, as the system is acidified to  $\text{pH} < 2$ , no aqueous Pd is seen, despite an increase in the amount of starting material in the aqueous phase.

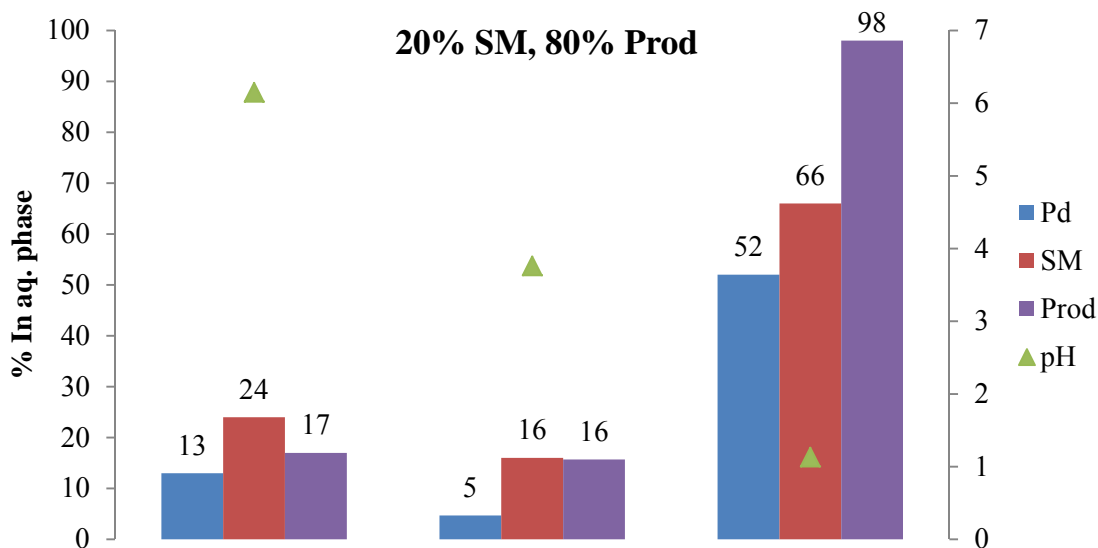
As a means of testing the effect that reaction product (5-methyl-2-phenylpyridine) would have on this partitioning, the same separations are made, but with varying amounts of reaction product present.



**Figure 4.48.** Control separation with 0.3 M of SM (5-methyl-2-bromopyridine) and Prod. (5-methyl-2-phenylpyridine). Separation performed in ACN,  $\text{H}_2\text{O}$ , and toluene mixture. HCl used to adjust pH.

Figure 4.47 shows that when equimolar amounts of starting material and product are present, separations at  $\text{pH} = 6.3$ ,  $3.7$ , and  $1$  give 10%, 8%, and 40% Pd, 12%, 15%, and 60% starting material and 5%, 60%, and 97% reaction product in the aqueous phase.

While this shows an increase in aqueous Pd, compared to when only starting material is present, it still does not reproduce the post-reaction separations seen with HCl.

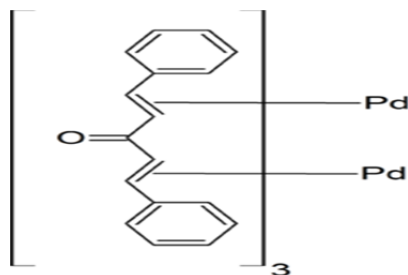


**Figure 4.49. Control separation with 0.06 M of SM (5-methyl-2-bromopyridine) and 0.24M Prod. (5-methyl-2-phenylpyridine). Separation performed in ACN,H<sub>2</sub>O, and toluene mixture. HCl used to adjust pH.**

Experiments were done with 0.06 M starting material and 0.24 M reaction product and 1 mol% Pd-tetrakis as a means of better imitating the amounts of starting material and reaction product present in post-reaction separations. Figure 4.49 shows these results. The aqueous amounts of Pd, product and SM are essentially the same as in Figure 4.48.

Neither control experiment using tetrakis are able to reproduce separation of Pd from reaction product using HCl following reaction (70% aq. Pd, pH ~4). A key difference in the control separations and separations following actual reaction is the larger amount of unoxidized phosphine present in the control separations. Table 4.2 shows increased phosphine amount can be detrimental to separation.

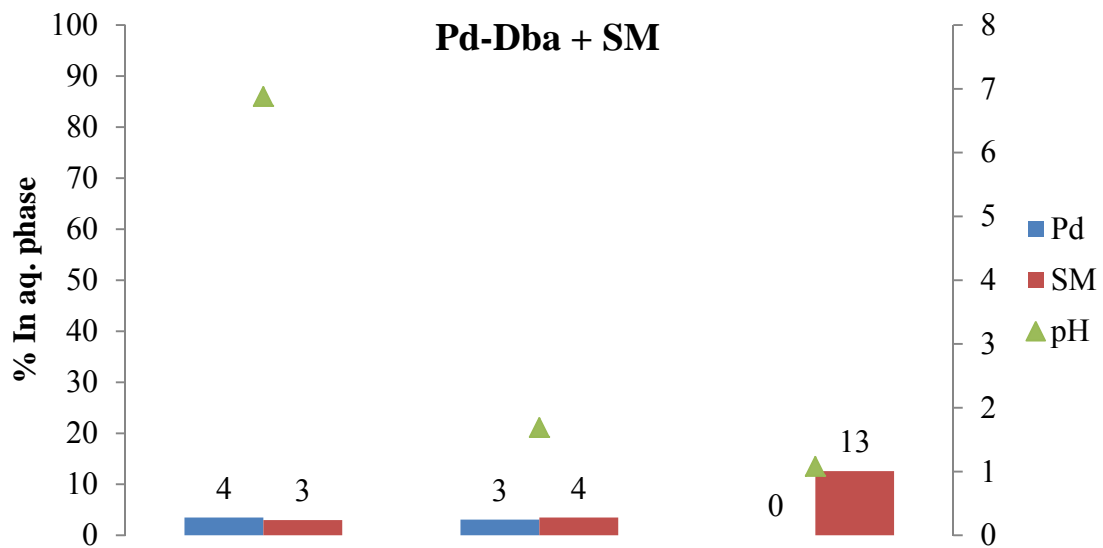
As a means of eliminating excess phosphine ligand, similar experiments were performed using Pd-DBA (Figure 4.50).



**Figure 4.50. Pd-DBA.**

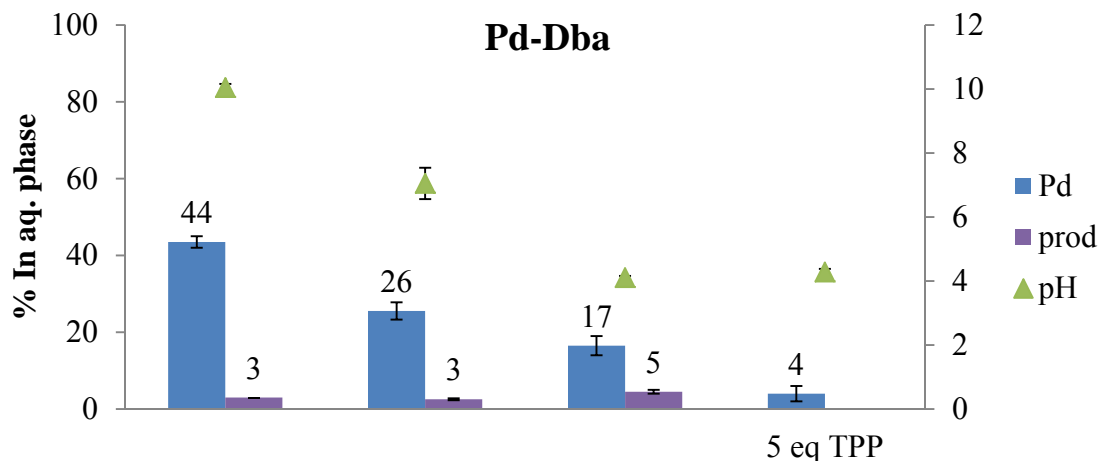
Figure 4.51 shows results of control separations with PdDBA and 5-methyl-2-bromopyridine. Water, acetonitrile, and toluene are added in a proportion meant to mimic that of the post-reaction separation experiments. 0.3M 5-methyl-2-bromopyridine, 1mol% PdDBA, and HCl are added to adjust reaction parameters. The Pd-DBA is chosen as a Pd(0) source which could potentially insert in the starting material. HCl is used to adjust the pH and potentially partitioning of the pyridine and Pd.





**Figure 4.51. Control separation with 1mol% Pd-DBa. 0.3 M SM= 5-methyl-2-bromo-pyridine.**

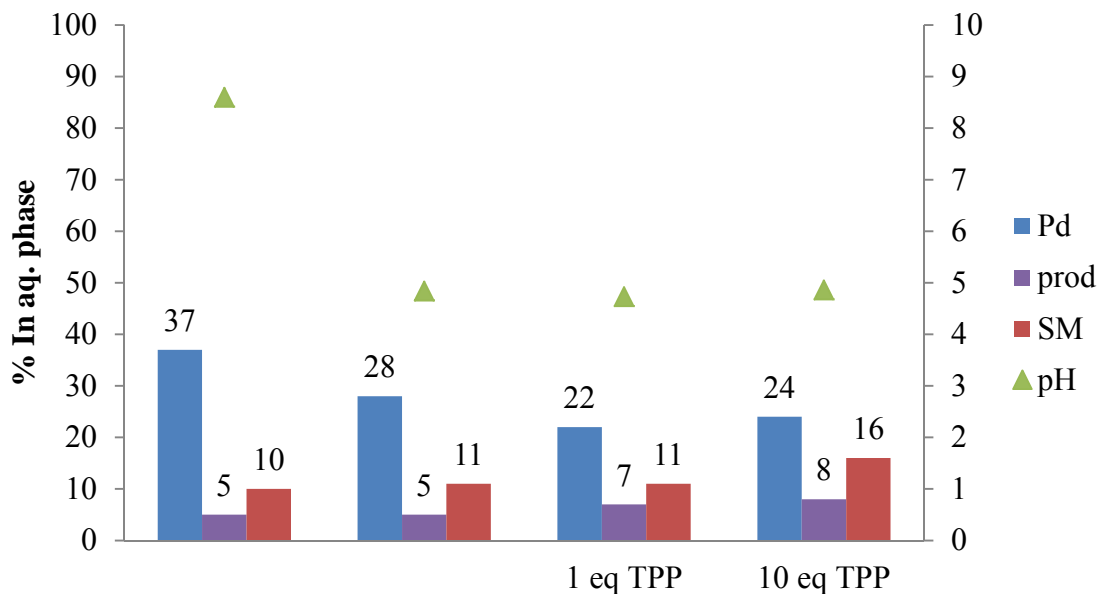
At no pH examined, are significant amounts of Pd or SM seen in the aqueous phase. This differs from separations seen post-reaction. The same experiment is performed but with 0.3M reaction product to isolate its role.



**Figure 4.52. Control separation with 1mol% Pd-DBa. 0.3 M Prod= 5-methyl-2-phenyl-pyridine.**

Figure 4.52 shows the results of this separation. At pH = 10, 7, and 4 give aqueous Pd amounts of 44%, 26%, and 17% of Pd in the aqueous phase with 3%, 3%, and 5% of reaction product in the aqueous phase. Interestingly, as the pH approaches 4, the amount of aqueous Pd decreases. This is opposite the trend seen where aqueous Pd amount increases as pH approaches the 4. Additionally, compared to the same separation with Pd-tetrakis (Figure 4.47), there is more aqueous Pd, confirming the detrimental effect of TPP. To further illustrate this, when 5eq of TPP are added, the amount of aqueous Pd decreases to 4%.

A control separation was also performed using Pd-dba (1mol%) in the presence of product (80%) and starting material (20%).



**Figure 4.53. “Control Separation” using 5-methyl-2-phenylpyridine (80%), 5-methyl-2-bromopyridine (20%), and Pd-DBA (1mol%) in ACN, H<sub>2</sub>O, and toluene. HCl is used to adjust pH.**

The results of this separation are shown in Figure 4.53. At pHs of 8.6 and 4.8, 37% and 28% of Pd, 5% of Product, and 10 and 11% of starting material are found in the aqueous phase. This does not agree with the results seen in Figure 4.28. Additionally, when 1 eq. and 10 eq. of TPP are added to the system, the amount of aqueous product and starting material are relatively unchanged. The amount of aqueous Pd is 22% and 24% under these conditions, not a large decrease from when no TPP is present.

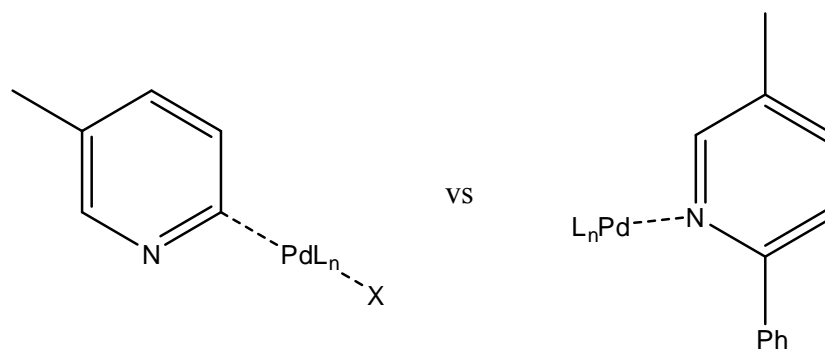
#### 4.4 Conclusions

This work shows that Pd catalyst can be effectively separated and recycled from coordinating reaction products produced by the Suzuki coupling reaction. Using OATS technology, both cysteine and EDTA are effective in removing 70-80% of palladium into the aqueous phase while >95% of the reaction product remains in the organic phase. The

reduction of solvent amount present during separation reduces the amount of Pd recovered in the aqueous phase to 67% and 48% with these two substrates. The addition of a wash step improves Pd recovery using EDTA to 80%. This amount of Pd recovery can be achieved using either CO<sub>2</sub> or toluene as an anti-solvent. Additionally, it is seen that this separated Pd can be recycled with a TOF comparable to the fresh reaction (21 h-1) when 5eq. TPP are added following separation.

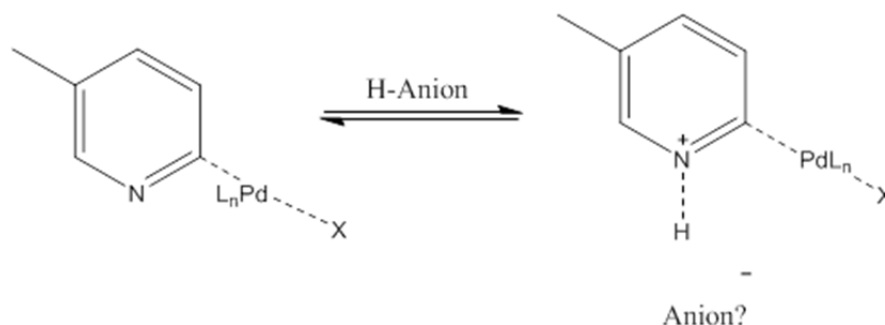
Further investigation into the separation shows the amount of Pd recovered in the aqueous phase can be duplicated by adjust the pH to 4-5 using acetic, formic, and sulfuric acid. This separated Pd can also be effectively recycled. However, at the same pH, separations using HI, HBr, trifluoro acetic acid, and benzoic acid are less successful. Thus, the pH of the system and the anion of the acid used both play important roles in the hydrophilicity of Pd in this separation system. Additionally, it was found that the amount of phosphine ligand present during separation makes the Pd more hydrophobic. Attempts to run control separations proved difficult to mimic the separation results seen following reaction, as none of the separations replicate the amount of aqueous Pd under similar separation conditions following reaction.

Based on these observations, there are multiple explanations as to what may be occurring in this separation.



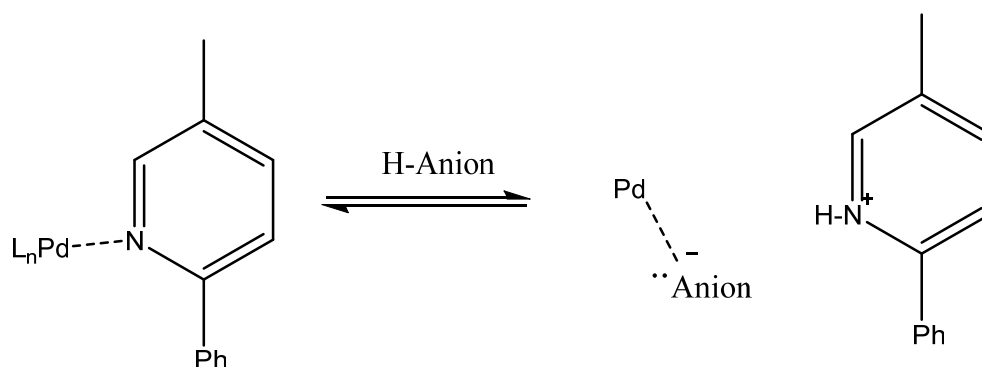
**Figure 4.54. Post-reaction catalyst state possibilities.  $L_n$  = TPP or reaction product.**

Figure 4.54 shows two possible post-reaction catalyst states that may explain the behavior seen in this separation system. The left image shows the catalyst inserted into the aryl-halo bond following reaction (the first step of the catalytic cycle). The second shows reaction product coordinated with the catalyst. In both cases, L represents either TPP or reaction product as ligand.



**Figure 4.55. Effect of acid addition. Inserted Catalyst**

Figure 4.55 demonstrates how the addition of acid would change the inserted-Pd complex. The pyridine would become protonated, making the entire complex more hydrophilic. The anion of the acid would then coordinate with this complex, thus the basicity/hydrophilicity of the anion would also play a role in the partitioning of Pd.



**Figure 4.56. Effect of acid addition: product complexation.**

Figure 4.56 demonstrates how the addition of acid would affect Pd bound to reaction product. The reaction product would protonate, thus de-ligating it from the Pd. The anion of the acid could then act as a ligand to the Pd, thus the basicity/hydrophilicity of the anion would affect Pd partitioning.

The fundamentals and versatility of this separation/recycle technique were probed by expanding the substrate scope. The basicity of the reaction product was found to be a key parameter in determining the effectiveness of separation. Separations of Pd from 2-phenylpyridine (pKa = 4.44) using HCl and EDTA give comparable recovery of aqueous Pd (~75%, pH ~4) to separation from 5-methyl-2-phenylpyridine (pKa = 4.73). Additionally, this separated Pd can be recycled with a comparable TOF with 10eq. of TPP added following separation.

Separations of Pd from 6-amino- and 4-amino-2-phenylpyridine ( $pK_a = 5.93$  and  $8.22$ ) are limited due to increased amounts of product in the aqueous phase (35% and 65% at pH of 4.8 and 7) presumably due to product protonation. In separations of Pd from 4-amino-2-phenylpyridine, increasing the pH to  $>9$  using base can significantly reduce the amount of reaction product in the aqueous phase 0%. The addition of 10eq. cysteine then results in 98% of Pd in the aqueous phase. Additionally, it was found that the use of very hydrophobic acids (perfluorooctanoic and dodecylbenzenesulfonic acid) result in very little reaction product (10% and 14%) at low pH (1.9 and 2.1). This indicates that the anion of the acid plays a role in the partition of the reaction product as well (Figure 4.37).

Separation of Pd from non-basic 4-phenylanisole and 5-cyano-2-phenylpyridine are unsuccessful for negligible amounts of Pd can be found in the aqueous phase at any pH examined. It is believed that a difference in catalyst state following reaction may explain this lack of success.

Overall, the work described in this chapter has demonstrated successful separation and recycle of Pd catalyst from coordinating Suzuki reaction products using inexpensive ligands and solvents. Further work has demonstrated that product basicity, pH of the separation, the anion used, and the final state of the catalyst all play pivotal roles in the partitioning of both Pd and reaction product in this system.

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## CHAPTER 5 - CONCLUSIONS AND RECOMMENDATIONS

### 5.1 Effect of CO<sub>2</sub> and pH on the Suzuki Coupling of Basic, Nitrogen-Containing Compounds

#### 5.1.1 Conclusions

Chapter 2 shows that efficient Suzuki coupling (quantitative yields) of the basic, 4-amino-2-halopyridine substrate can be achieved with inexpensive ligands and solvents by running reaction under CO<sub>2</sub> pressure with an appropriate amount of solvent. Interestingly, less-basic 2-halopyridine substrates perform poorly under these same conditions.

Further study reveals that it is the pH of the system that causes the observed phenomena. The addition of CO<sub>2</sub> causes acid-base reactions in the aqueous phase, effectively buffering the reaction system at a pH of about 8. Work demonstrates that reaction of 4-amino-2-halopyridine achieves quantitative yield at this pH with or without CO<sub>2</sub>. Conversely, reactions of 2-halopyridines react poorly at this same pH regardless of the gaseous environment. Reactions under N<sub>2</sub> at various pH points build on this observation to demonstrate that a substrate-specific reaction pH exists. (Figure 2.22).

A study of reaction progress over time reveals that 4-amino-2-chloro- and 4-amino-2-bromopyridine react at the same rate under CO<sub>2</sub> pressure, and increasing CO<sub>2</sub> pressure and phenylboronic acid amount increases this reaction rate.

An examination of earlier (<1 h) time periods of these reactions shows that reactions run at pH of both 8 and 12 achieve ~20% yield of product within 5 minutes. The more basic reaction essentially stops at this point, while less basic reactions proceed to quantitative yields. It is believed that this is indicative of catalyst poisoning of Pd by reaction product when the pH is ~12, but when the pH is ~8 protonation of reaction product prevents product coordination with the catalyst.

#### 5.1.2 Recommendations

The catalyst loading of the reactions in Chapter 2 offer an opportunity for improvement. The protocol described leads substantial improvement in the reactivity of basic, nitrogen containing heterocycles; however, the catalyst loading (5 mol%) is quite high. Further work could be done to attempt to reduce this loading of catalyst.

The effect of pH on the reaction system could also be better understood. While data presented in Chapter 2 supports the conjecture of how pH increases the reactivity of the Suzuki coupling of 4-amino-2-halopyridines, further work could be done to clarify the pH effect. <sup>15</sup>N-NMR could prove beneficial in observing N-Pd ligation at various pH's in the reaction system.

Additionally, while Figure 2.22 shows a trend between reaction pH and reaction yield based upon substrate additional, work could be done to better understand this relationship. 1). reactions yields could be obtained at more pH points to fill out additional points on the graph. 2). Expansion of the substrate scope would be valuable. Testing the effect of pH on the Suzuki coupling of a wider array of substrates could help better

understand the role pH plays in the reactions system and test the versatility of using pH as a means of tuning the reactivity of Suzuki reactions.

Finally, the successful reaction of basic, aminopyridines at a close to neutral pH of 8 calls into question the role of base in the reactions system. A study of base-free Suzuki coupling reactions would be a novel and interesting avenue that could be pursued.

## **5.2 Palladium Recovery Using Organic-Aqueous Tunable Solvents (OATS)**

### **5.2.1 Conclusions**

Chapter 3 shows that the use of Organic/Aqueous Tunable Solvents is an effective method for the separation of homogeneous palladium from the organic product (5-methyl-2-phenylpyridine) of a Suzuki coupling reaction. This technique is particularly desirable for successful separation is achieved with inexpensive ligands and solvents. Investigation reveals that careful additive selection is crucial to the success of separation. OATS separation with no additive used gives very little Pd in the aqueous phase, while hydrophilic, chelating sulfur additives and hydrophilic chelating polyacids are successful in moving Pd to the aqueous phase. Among additives screened, cysteine stands out as the most promising choice for increasing the hydrophilicity of palladium. When using cysteine, a dependence of palladium removal on additive loading has also been demonstrated, varying from 10% palladium removal with no additive to 74% palladium removal when 20 equivalents are used under 200 psi of CO<sub>2</sub>. Furthermore, tunable separation using cysteine has been demonstrated as a function of CO<sub>2</sub> pressure, varying palladium removal from 63% at 100 psig to 80% at 400 psig. Finally, the ability of activated carbon to extract the palladium from the catalyst-rich aqueous phase has been

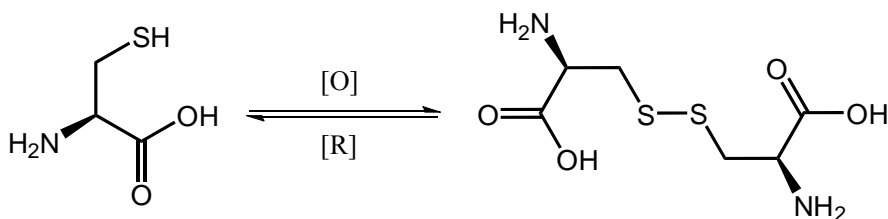
demonstrated, highlighting the capability of this process to be immediately implemented into existing technologies in a manner that adheres to the principles of green chemistry and engineering.

In addition to these findings, the substrate scope of the OATS-sulfur additives process has been examined by investigating separation of Pd from 4-amino-2-phenylpyridine. This substrate expansion indicates that the basicity of the reaction product plays a key role in its partitioning due to formation of carbonic acid from dissolved CO<sub>2</sub> acting as a proton source. This suggests that pH could be used in addition to CO<sub>2</sub> pressure as a tunable parameter for separations of Pd from basic Suzuki products.

#### 5.2.2 Recommendations

While the OATS-cysteine separation provides the most successful separation results, the presence of this sulfur-chelant offers challenges when considering recycling the separated catalyst. Suzuki coupling reactions carried out in the presence of cysteine afford negligible yield, indicating that cysteine complexes with and effectively “poisons” the palladium catalyst. While this behavior is useful toward the generation of a hydrophilic catalyst species, it greatly shortens the lifetime of the catalyst compared to a process that incorporates catalyst recycling.

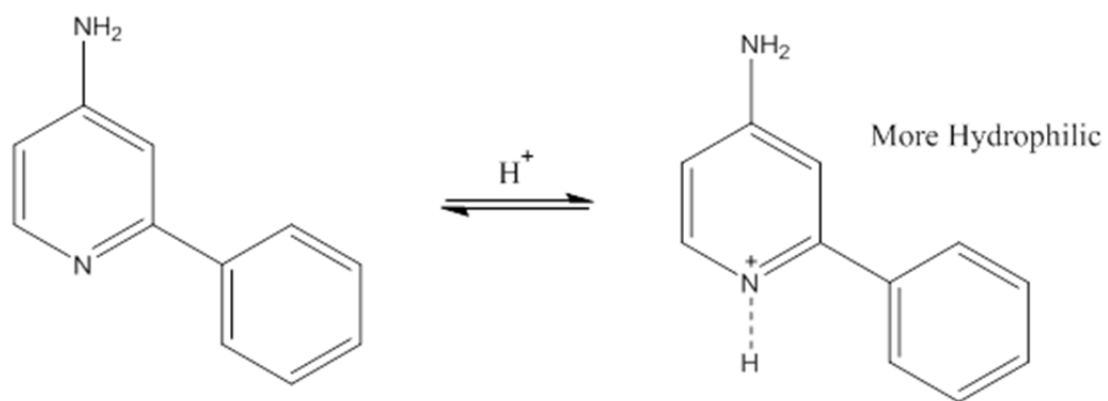
One possible solution may be the oxidation of cysteine to cystine, shown in Figure 5.1.



**Figure 5.1. Oxidation of Cysteine to Cystine.**

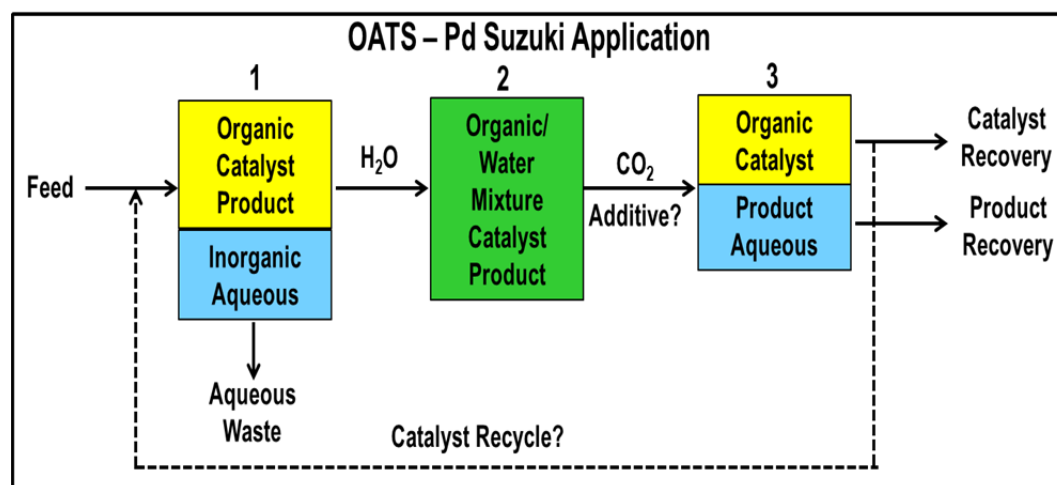
Literature shows evidence of hydrogen peroxide to oxidize cysteine to cystine.<sup>1</sup> Oxidation of cysteine could prove effective in de-ligating cysteine from the catalyst, thus allowing it to perform further chemistry.

While this work shows that the protonation of more basic Suzuki reaction products (4-amino-2-phenylpyridine) offers a limitation when trying to separate Pd into the aqueous phase, a potential solution exists.



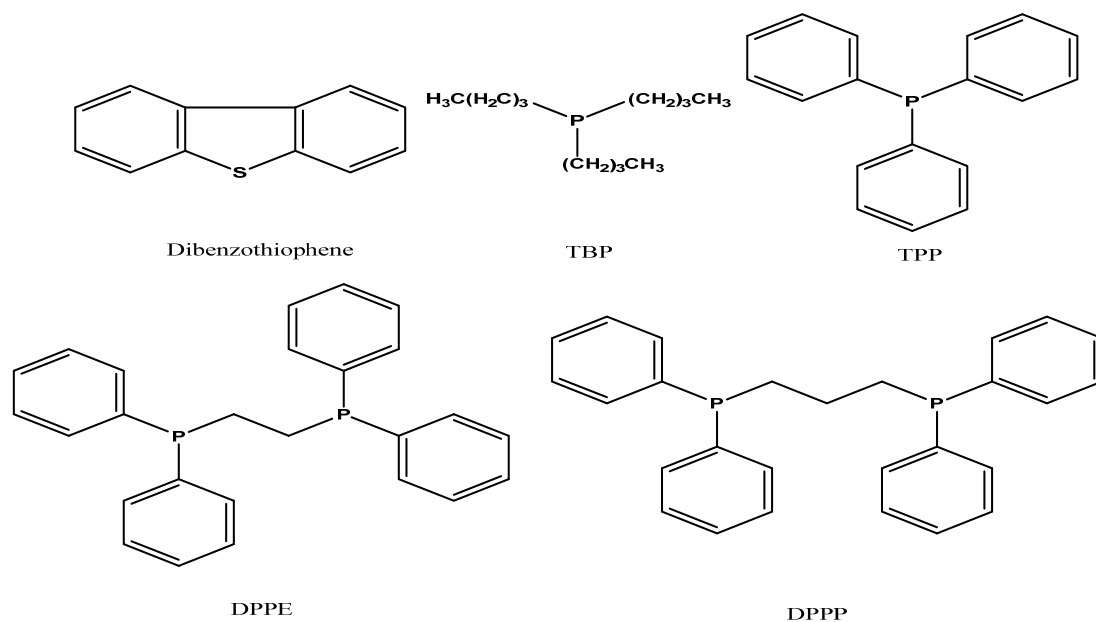
**Figure 5.2. Protonation of 4-amino-2-phenylpyridine.**

The increased hydrophilicity of more basic reaction products offers a potential path forward. The pH of the separation system could be tuned to protonate more of the reaction product (Figure 5.2), partitioning more of this product into the aqueous phase. A hydrophobic additive could then be used to partition Pd into the organic phase (Figure 5.3) allowing for effective separation.



**Figure 5.3. Hydrophobic Pd OATS scheme.**

Figure 5.4 shows a selection of relatively inexpensive, hydrophobic ligands which could potentially serve as additives for this type of separation.



**Figure 5.4. Potential Hydrophobic Additives**

### 5.3 Recycle of Pd Using Smart Solvents

#### 5.3.1 Conclusions

Chapter 4 demonstrates successful separation of Pd catalyst following the Suzuki coupling reaction of 5-methyl-2-phenylpyridine with phenylboronic acid in acetonitrile/water using a triphenyl phosphine ligand, inexpensive additives and inexpensive solvents. Separation can be achieved using smart solvent technology with  $\text{CO}_2$  or toluene as anti-solvents and EDTA (acidic), HCl, acetic acid, sulfuric acid, or formic acid as additives. These separations result in 70-80% of palladium into the aqueous phase while >95% of the reaction product remains in the organic phase at a pH of 4-5. Solvent amount and the use of a wash step are also proven to be key parameters in this separation. This work also shows that this separated Pd can be recycled with a TOF comparable to the fresh reaction ( $21 \text{ h}^{-1}$ ) and that the amount of TPP added following



separation is a key parameter. Interestingly, at a pH of 4-5, separations using HI, HBr, trifluoroacetic acid, and benzoic acid are less successful, indicating that the anion of the acid used and the pH of the system play important roles in the hydrophilicity of Pd in this separation system. Additionally, it was found that the amount of phosphine ligand present during separation makes the Pd more hydrophobic. A more detailed explanation as to how the separation is effected by these factors is given in section 4.4.

The fundamentals and versatility of this separation/recycle technique were probed by expanding the substrate scope. This study demonstrated that the basicity of the reaction product is a key parameter separation. Separations of Pd from 2-phenylpyridine using HCl and EDTA gave comparable recovery of aqueous Pd (to separation from 5-methyl-2-phenylpyridine. Effective recycle of this separated Pd is also demonstrated.

Separation of Pd from the more basic 6-amino- and 4-amino-2-phenylpyridine ( $pK_a = 5.93$  and  $8.22$ ) is limited due to increased amounts of product in the aqueous phase (at pH of 4.8 and 7), presumably due to product protonation. However, it was shown that the combination of a higher pH ( $>9$ ) and cysteine can be used to effectively separate Pd from 4-amino-2-phenylpyridine. Interestingly, it was found that the use of very hydrophobic acids (perflourooctanoic and dodecylbenzenesulfonic acid) result in very little reaction product (10% and 14%) at low pH (1.9 and 2.1), indicating that the anion of the acid plays a role in the partition of the reaction product as well (Figure 4.37).

Separation of Pd from non-basic 4-phenylanisole and 5-cyano-2-phenylpyridine also proved unsuccessful by this technique, for negligible amounts of Pd can be found in the aqueous phase. It is believed that a difference in catalyst state following reaction may

explain this lack of success. Increased amounts of Pd bound to phosphine, nanoparticle formation, catalyst not inserted in the aryl-halo bond are all considered as possible explanations.

Overall, the work described in Chapter 4 demonstrates a novel, successful separation and recycle of Pd catalyst from coordinating Suzuki reaction products using inexpensive ligands and solvents. This work also demonstrates that this process very substrate specific and that the pH of the separation, the anion used, and the final state of the catalyst all play pivotal roles in the partitioning of both Pd and reaction product in this system.

### 5.3.2 Recommendations

There are several areas of study which could build upon the results in Chapter 4. This work has hypothesized what is occurring at a molecular level in this separation; however, characterization of the post-reaction catalyst could provide more insight into this issue. Techniques such as EXAFS,  $^{15}\text{N}$  and  $^{13}\text{C}$ -NMR, high-resolution mass spectrometry, and crystallization could all prove beneficial in determining the oxidation state of the catalyst and the ligands bound to the catalyst. This knowledge could be applied to existing data to give a definitive explanation as to how this separation works. Additionally, TEM could be used to examine palladium nanoparticle formation following reaction of less basic substrates (5-cyano-2-bromopyridine, 4-bromoanisole). This could serve as an explanation as to why it is difficult to separate palladium from the product of these reactions.

Additionally, it has been shown that the presence of TPP can hinder Pd separation. Investigating separation following Suzuki reaction with less TPP or longer

reaction times (to increase TPP oxidation) could prove effective in increasing the amount of Pd recovered in the aqueous phase.

Separation of Pd from 5-cyano-2-phenylpyridine and 4-amino-2-phenylpyridine is successful using cysteine; however, recycle of this catalyst is unsuccessful. A potential solution to this issue is oxidation of cysteine. This is discussed in 5.2.2.

Another possible technique of separating Pd from 4-amino-2-phenylpyridine is recover of the product into the aqueous phase and Pd catalyst into the organic phase. This technique is also discussed in 5.2.2.

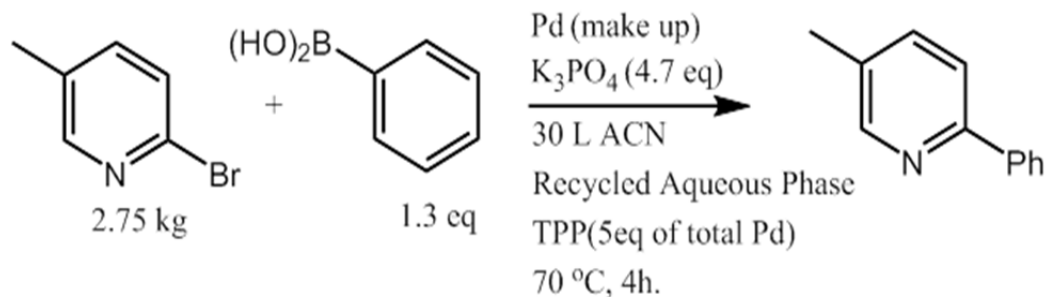
Finally, as separation using this technique has proven very substrate specific, expanding this separation to other Suzuki reaction products could further test the versatility of this technique and potentially provide more insight into the fundamentals of this separation system.

## 5.4 References

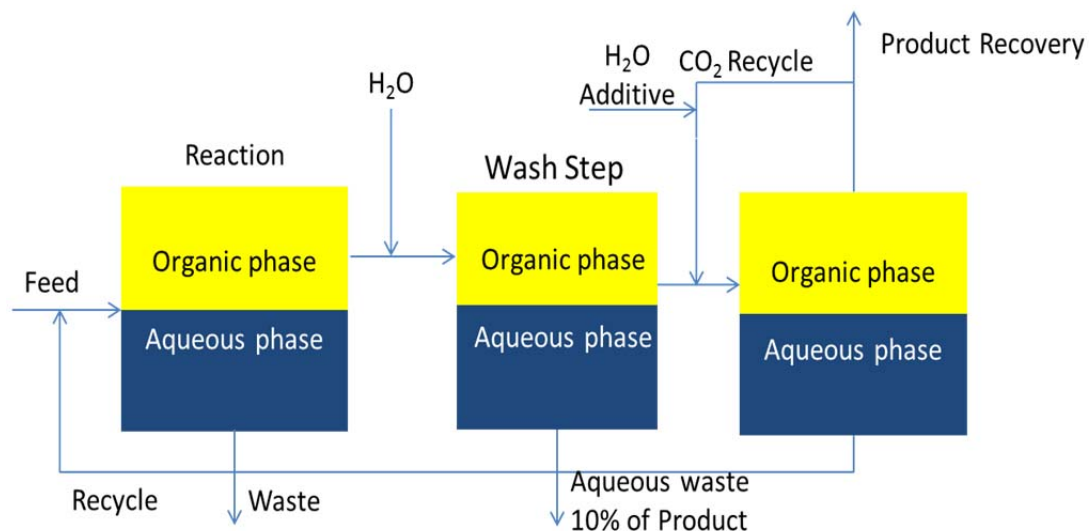
- (1) Kendall, E. N., F. *J Biol Chem* **1926**.

## APPENDIX A - PROCESS MASS INTENSITY AND PROCESS COST INTENSITY OF SEPARATION AND RECYCLE OF CATALYST

Multiple additives and anti-solvents have been examined for a separation and recycle process using smart solvents. As a method of comparing the relative success of each of these processes, data from the preceding sections is used to calculate a theoretical process mass intensity (PMI, kg/kg-product produced) and process cost intensity (cost(\$)/kg-product produced). The calculations focus on the separation and recycle of palladium from 5-methyl-2-phenylpyridine reaction product following recycle reaction (Figure A.1) using CO<sub>2</sub> or toluene as anti-solvents, and EDTA/HCl/ or cysteine as an additive for separation. Calculations are performed on the basis of a 2.75 kg feed of 5-methyl-2-bromopyridine (1000 times the scale used experimentally). Data from Separation and recycle performed on fresh reactions in previous sections is used to give a rough estimate of material amounts necessary to continuously separate and recycle Pd catalyst.

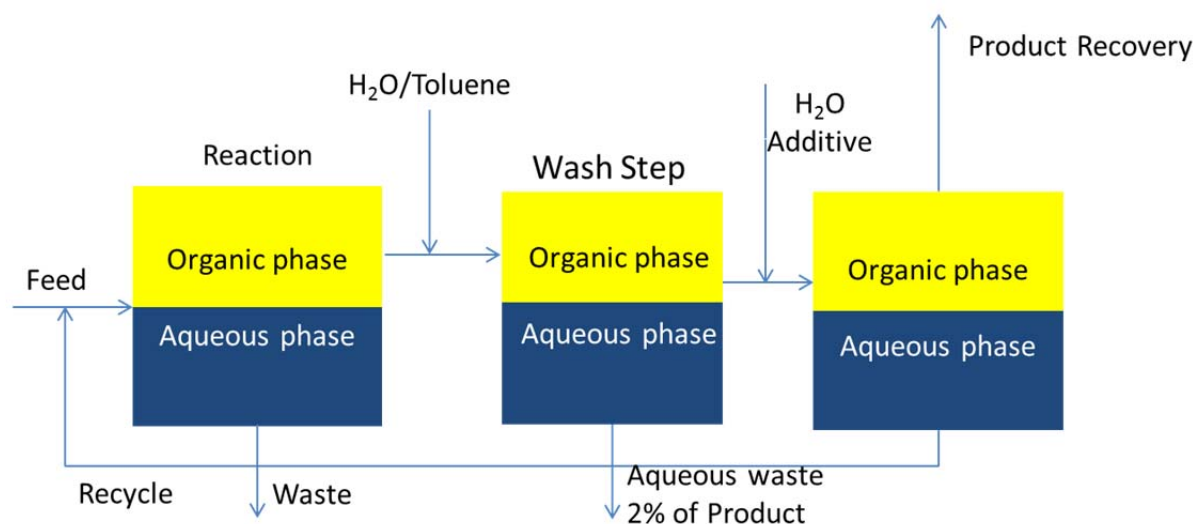


**Figure A.1. Steady-state recycle reaction.**



**Figure A.2. Steady-state CO<sub>2</sub> Separation and Recycle**

Figure A.2 shows the process schematic for a separation and recycle of Pd from reaction product using CO<sub>2</sub> as anti-solvent. Fresh phenylboronic acid, starting material, base, acetonitrile, TPP ligand, and make-up catalyst are added to recycle reaction. A wash step is then performed resulting in loss of 10% of product in the post-reaction mixture in the waste aqueous phase. CO<sub>2</sub> is then applied (here recycle of CO<sub>2</sub> is assumed) along with additive and fresh water to perform separation.



**Figure A.3. Steady-state Toluene Separation and Recycle.**

Figure A.3 shows the schematic using toluene as anti-solvent, the key difference from CO<sub>2</sub> separations is that 1) the anti-solvent is not recycled and 2). Toluene is added prior to the wash step reducing product loss.

$$\begin{aligned} \text{molrxnproduct} &= \text{rxntime} * (\text{TOF} * \text{RC} + \text{TOF} * \text{FC}) \\ \text{RC} &= \% \text{Sep} * (\text{FC} + \text{RC}) \end{aligned}$$

**Equation 5.1. Equations for calculation of feed and recycle catalyst amounts at steady-state. TOF = turnover frequency of catalyst. RC = mol recycled catalyst at steady state. FC = mol make-up catalyst in feed as steady-state. %Sep = % of post-rxn catalyst separated into the aqueous phase.**

Since the process is assumed to be in steady-state. **Error! Reference source not found.**A.4 is used to calculate the amount of catalyst recycled (RC) and in the feed (FC)

based upon the turnover frequency of both recycled and separated catalyst (TOF), the amount of desired reaction product (85% yield, 13.6 mol), and the % of catalyst separated following reaction (%Sep). TOF values ( $\text{h}^{-1}$ ) used in calculation are 21 for feed catalyst, 21 for catalyst separated by EDTA, and 27 for catalyst separated by HCl. % Separation values are 70% for HCl, 75% for 5eq. EDTA, and 83% for 20 eq. EDTA. With these values calculate it is possible to calculate the PMI (kg/kg-product, **Error! Reference source not found.**) of each process.

$$PMI = \frac{\text{Mass of materials}}{\text{Mass of product}}$$

#### **Equation 5.2. Process Mass Intensity (PMI)**

Additionally, cost data can be used to calculate the PCI (\$/kg-product) based upon materials used. This PCI does not include energy costs, labor, product purification, etc. and is purely and estimating based upon the material balance of each process. Costs of materials were obtained from vendors Sigma Aldrich and Matrix Scientific. The cost of Pd was obtained from APMEX.com. If a price could be found for quantities >0.5kg, this was used as the cost of material per kg. For materials whose prices could only be found for amounts <0.5kg, a 0.6 economy of scale was used to estimate the cost of the material. The costs are seen in Table A.1.



**Table A.1. Cost of Materials Used**

<b>Compound</b>	<b>Cost(\$/kg)</b>
TPP	259
Pd	20000
Cysteine	518
EDTA	168
ACN	44.5
5-methyl-2-bromopyridine	328
5-methyl-2-phenylpyridine	7150
HCl	12
Toluene	38
K <sub>3</sub> PO <sub>4</sub>	46
Phenylboronic Acid	68
Water	22

With costs known, the PCI of each process can be calculated on a \$ cost per kg product produced basis by **Error! Reference source not found.**

$$PMI = \frac{CostofMaterials(\$)}{Massofproduct(kg)}$$

**Equation 5.3. Process Cost intensity.**

The PCI and PMI values are shown in Table A. The process which leads to the lowest PMI and PCI is a separation and recycle where toluene and HCl is used for separation. Despite giving the lowest amount of Pd separated and recycled it has the lowest PMI and PCI. This is primarily due to the reduction in product loss in the wash step and price/mass difference in EDTA and HCl.

**Table A.2. PMI and PCI of processes.**

<b>Anti-Solvent</b>	<b>Additive</b>	<b>Eq.</b>	<b>PMI (kg/kg product)</b>	<b>PCI (\$/kg Product)</b>	<b>Profit (\$/kg Product)</b>	<b>% Pd Sep/Recycled</b>
CO <sub>2</sub>	EDTA	5	41.3	1900	5250	75%
CO <sub>2</sub>	EDTA	20	41.6	1940	5210	83%
CO <sub>2</sub>	HCl	10	41.2	1880	5270	70%
Toluene	EDTA	5	39.8	1820	5330	75%
Toluene	EDTA	20	40.1	1860	5290	83%
Toluene	HCl	10	39.8	1800	5350	70%

It is likely that the prices used for solvents and additive are still far higher than what would be seen on a bulk scale relative to bulk Pd costs, for the bulk Pd stream still only represents ~5% of total costs. The price at which the theoretical product would be sold would also be lower, thus lowering profits accordingly. Additionally, solvent could likely be recycled (which would add costs for solvent separation). Thus, the PCI should be viewed with skepticism. However, the PMI is more accurate and is relatively close between all of the methods evaluated.

**Table A.3. Processes in terms of Pd Feed Cost**

<b>Anti-Solvent</b>	<b>Additive</b>	<b>Eq.</b>	<b>PMI (kg/kg product)</b>	<b>Pd Feed Cost (\$/kg Produced)</b>	<b>% Pd Sep/Recycled</b>
CO <sub>2</sub>	EDTA	5	41.3	85	75%
CO <sub>2</sub>	EDTA	20	41.6	58	83%
CO <sub>2</sub>	HCl	10	41.2	84	70%
Toluene	EDTA	5	39.8	85	75%

Toluene	EDTA	20	40.1	58	83%
Toluene	HCl	10	39.8	84	70%
CO <sub>2</sub>	Cysteine	20	35.7	340	no recycle

Given that bulk prices of additive and solvent are more difficult to find, Table A.3 gives a better idea of the cost-savings of each process. Separation and recycle using 20 eq. of EDTA recycles the most (83%) Pd of any of the processes, thus resulting in a catalyst cost of \$58/kg-product produced. The decision of whether to use CO<sub>2</sub> or toluene would likely hinge upon the relative cost of purifying the product vs. building more expensive pressure vessels for separation of catalyst from product. The economic benefit of this separation and recycle process is evident when compared to separations with cysteine, in which Pd-recycle is not possible. This results in a cost of \$340/kg-product of palladium in the feed stream.